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THE COMMUNITY RESPONSIBILITY FOR THE CARE OF THE MENTALLY RETARDED

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UNTIL relatively recently, the contribution of even the more progressive communities toward meeting the problem of community care for the mentally retarded has been confined primarily to a limited number of special classes for the minimally retarded of school age (usually from 6 to 16 years) academically structured, and rarely oriented toward preparing this category of the retarded for eventual integration into a competitive industrial world. Also provided in most states are residential institutions designed primarily to segregate those with potential antisocial possibilities as well as the moderately and severely retarded, often grouped together and only rarely fulfilling the objectives implied in their title of "Training Schools." Although professional personnel in this field have long been aware of the inadequacies inherent in these two facilities for meeting the over-all problem, it was undoubtedly the relatively recent development of organized and intelligently led parent groups that have been responsible for stimulating the crystallization of ideas from many sources into what still remains for most of us the blueprint stage of effective community care.

The problem is naturally complex for at least five reasons:

1. The range of intellectual defect in our retarded population varies from the most profound, with I.Q. of less than 10, up to levels that merge almost imperceptibly with the normal. These require widely varying objectives and techniques in management. Fortunately the largest group in the community, making up at least 75 per cent of the total retarded population, are minimally involved with I.Q.'s between 50 and 75. Experience has shown that most of these are responsive to training and supervision and can be successfully integrated into an industrial or rural society.

2. In the absence of adequate programs, especially in the face of an expanding urban and industrialized society, the tendency toward the development of antisocial and deviant

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behavior is increased. The management problems under these conditions are multiplied, as might be expected. Unfortunately, too many communities find themselves faced with this handicap as well. The necessity for segregation under these conditions is increased and the expense of any such program greatly magnified.

3. Since brain injuries and cerebral malformations are important causes of mental retardation, there is a high incidence of associated defects such as cerebral palsy, convulsive disorders, and sensory abnormalities in the group as a whole, although more marked in the more seriously retarded. In addition, basic defects in personality structure attributable to organic cerebral pathology complicate the picture in many. These defects obviously add to the management problems, requiring specialized services and supervision.

4. Every retarded child is a member of a family group, and its presence in the group creates problems of a social and psychogenic nature that must be met and solved. No community program can be really effective for the retarded unless the integrity and stability of the family is preserved.

5. Communities vary greatly in size, predominant cultural characteristics, employment and recreational possibilities, and other aspects, as well as its rural or urban nature. These will all influence the extent and complexity of any over-all program.

It is obvious for these reasons and others that only in the most general way can a program for the retarded be described. Before discussing the individual needs of the three basic categories, there are certain general services and facilities that have application to all levels of defect.

Diagnostic, guidance, and social service facilities and services:

1. Diagnosis involves at least three basic considerations. First, it is essential to rule out any other condition that may be responsible for the deviant development and behavior. This is fundamentally a problem in differential diagnosis and includes consideration of such conditions as auditory and visual defects; aphasias and other language disabilities; motor defects of cerebral origin, that is, cerebral palsy; environmentally induced behavior and emotional problems; and finally the possibility of primary, organically induced, personality deviations. Second, although the management of a retarded child is only rarely influenced by the etiology and depends basically on current status, for purposes of family counseling it is essential. Moreover, if preventive measures are ever to gain practical application, it will be through the detailed investigation of etiological possibilities. Much of the diagnostic studies are therefore designed to meet this aspect of the problem. Third, the diagnostic evaluation is also aimed at the discovery of associated physical defects so that proper therapeutic or preventive measures may be applied. This will include a medical consideration of all the organ systems as indicated.

It is apparent that these three aspects of diagnosis are basically medical responsibilities, although requiring the assistance of other disciplines. Moreover, the diagnostic medical facility must be well equipped and

well staffed to provide the means for the frequently extensive investigations and consultative services required. For these reasons, the diagnostic center is best placed and integrated into a modern hospital or medical school environment where it can also serve as a source of student and intern training. Since the diagnostic evaluation rarely requires more than a single visit or at most a short-term observation, it should rarely be necessary to duplicate this service elsewhere except in the case of the largest and most populous states.

2. Guidance and social services, on the other hand, depend for their effectiveness on a more or less continous contact with the child and the family involved. These services must, therefore, be widely distributed so that, for many, it can actually be brought into the home. Much of these services can be performed by nonmedical personnel. For this to be successful, however, these must be extremely well oriented through the original medical and guidance contact and through their knowledge of local facilities, and must have constantly available medical sources either locally or from the diagnostic center for consultation and advice. Much of these services can be maintained through already established facilities like the local family services, public health nursing, and social welfare organizations. Occasionally, if necessary, these special services must be established. In any case, some centralized coordination, most effectively located in the diagnostic center, must be supplied. It is important to mention here the necessity for including the local family physician or pediatrician in such a guidance program. This also will require a conscientious effort on the part of the diagnostic center toward his complete orientation along pertinent lines referable to his patient. Need I say that such contacts involving specific cases and problems, if properly utilized, can serve over the years as a most effective form of medical education for the practicing physician in this highly specialized field. While the centralized diagnostic center and its associated guidance and social service functions and coordinating responsibilities will as a rule require considerable space and staffing, the smaller and widely distributed guidance units will vary greatly in size, depending on the area to be covered and the load to be serviced. In some of the smaller communities it may require no additional space at all, and can be incorporated into the function of the local public health nurse.

We may now turn to the more specialized community needs of the varying categories of the retarded population. For this purpose, the retarded may best be classified into three groups: (1) the high grade, minimally retarded, also called the educable, whose intellectual status roughly varies between I.Q. of 50 to 75; (2) the middle grade, moderately retarded or trainable, with I.Q. ranges of from 25 to 50; and (3) the low grade or severely retarded, with I.Q. less than 25.

Group I. The high-grade retardate represents the largest category and probably accounts for at least 75 per cent of the over-all problem. Under the proper conditions of family care,

education, training, and supervision, it should be possible to eventually successfully integrate most of this group into the industrial or farming community. Our failures in the past with this group can, in great part, be traced to the lack of community resources. To place the major responsibility for the rehabilitation of these children on the family alone, as has been and continues to be true in large sections of the country, simply invites poor results. A coordinated program for this category of the mentally retarded should include the following:

1. Special classes in the elementary schools have been widely accepted by most public school systems as a means of meeting the educational needs of these children. Considerable progress has been made in developing effective techniques and programs and in defining acceptable goals. These facilities, of which there is still a significant shortage, have, in general, been successful in the management of the young child. They have failed, however, to meet the needs of the adolescent and teenage group as regards the problems of occupational training and in supplying effective socializing experiences to help meet the ultimate goal of social and industrial integration. For this purpose, special classes on the secondary school level and in the vocational schools are essential. This type of educational program is only rarely encountered at present and considerable administrative and technical experience need to be obtained for developing the most effective approach along these lines.

2. One of the major weaknesses in the management of these children, even in the more enlightened communities, has been the failure to maintain some type of supervision for these high-grade retardates after leaving the protected environment of the public schools at 16 or 18 years of age. This should include some degree of job counseling, job finding, and placement. It should also include the orientation of the job foreman or immediate supervisor. It also involves assistance in the effective budgeting of whatever salary is earned. It further requires recreational supervision to guide these activities into acceptable social channels. All these would appear to be legitimate responsibilities of the guidance and social services previously described, and indicates the need for close cooperation between these services and the school systems.

3. An over-all program of the above type or some acceptable approximation should make it necessary to remove from the home and institutionalize only a very small number in this category. Such a solution, that is, institutionalization, should be reserved for the following indications:

(a) The presence of a serious behavior problem or basic personality disorder which makes community adjustment impossible and potentially hazardous and for which the usual psychotherapeutic procedures have not been effective. In these cases, the more structured environment in association with intensive psychotherapy at the institution may require a relatively short period of commitment only.

(b) A completely unsatisfactory home environment and the unavailability of a suitable foster home occasionally necessitates institutionalization. Social work with the family while the child is away may reduce the need for extended separation.

(c) Probably the major factor responsible for institutionalization in this category of retardate in most cases is the complete absence or inadequacy of community facilities to meet his problem and the subsequent development of potentially asocial behavior. The separation of a child from his family for these reasons is an unfortunate result of community failure to meet its responsibility. It might also be stressed that from the point of view of public finances, to institutionalize a child because of paucity of community facilities represents the most expensive and usually least satisfactory method of meeting this problem on a long-term basis.

Group II. The middle-grade or moderately retarded group makes up approximately 20 per cent of the overall problem. We may consider the mongoloid child as one point of reference in this category since this clinical group probably represents close to half of the total number of middle-grade retardates. While the high-grade retarded child can rarely be definitely diagnosed as such much before the fourth to the sixth year, and even then one hesitates to be too dogmatic in prognosis, the middle grade can be identified much earlier, sometimes in infancy, and in the case of the mongoloid, in most instances at birth. This brings the child to the attention of diagnostic and guidance services at a time when the nature of the advice as to management may be crucial in determining the subsequent life history of the child and family. I refer especially to the tendency on the part of some pediatricians or medical practitioners to recommend either directly or through more or less subtle indirection the separation of the child from the family at birth or soon thereafter. In relatively rare situations such a move may have to be seriously considered. As a routine measure it must be condemmed in the strongest manner. The importance of the early mother-child relationship for the healthy development of a personality structure in line with the intellectual capacity has just as many implications for the moderately retarded as for the normal child, and, in many respects, probably more. This is true even though for many institutionalization must still remain the eventual solution.

The problem of the community management of the moderately retarded is, at the present time, in a great stage of flux. That these children with few exceptions cannot be successfully integrated into our usual social environment in the absence of even minimal community facilities is probably true. To what extent a comprehensive community program especially designed for this type of child will lead to more successful adjustment and possibly permanent integration remains to be seen. While the complete answer is yet to be found, the need for a community program to care for the present problem cannot be denied. In isolated parts of the country, excellent programs have been developed. As yet, most must be considered experimental until more long-term information as to the results in terms of successful integration is obtained.

That for a reasonable proportion of the moderately retarded proper community supervision and programs may reduce significantly the need for universal, eventual institutionalization, or may shorten the period for such need, is, in my opinion, very likely. It must be admitted that this personal impression for lack of other sources is based on the progress of numbers of these children in an institutional setting and exposed to a program designed especially for this type of child. Whether such a program will be equally successful in a community setting remains to be seen.

A comprehensive program for the moderately retarded should include the following:

1. Day-care centers or specialized kindergartens: While this type of facility is of considerable value for the normal or minimally retarded child as preparation for the more academic school environment, for the moderately retarded child it has a vital importance. If our public school system is to be stimulated to accept this type of child for educational care, it should be aided by the preliminary preparation in socialization and behavior that a day-care center would afford. At the present time many facilities of this type are supported by parent groups. That eventually public support and supervisory administration will be required is likely.

2. Specialized classes and facilities in the public schools: These must not be confused with the special classes for the minimally retarded; attempts at combining these two categories of the retarded will rarely be successful. It is my conviction that, while there may be legitimate differences of opinion as to where the responsibility for maintenance of day-care centers should reside, the administration of these special classes is undoubtedly the responsibility of the public school system and best administered through that source. For the older child, where the intellectual capacity will allow, facilities for industrial training on simplified lines, socializing experiences, and recreational opportunities should be provided through these means.

3. Sheltered workshops: These provide an opportunity to utilize the limited industrial capacity of the adult moderately retarded under the close supervision this group requires. While frequently these facilities can be maintained on a self-liquidating or profit-making basis, financially it is a serious mistake to consider this as the prime purpose. Its major importance must be its function as part of the community program that will aid in successfully maintaining this category of retarded in those families who are able and desire to do so. At the present time, the few facilities of this type in operation have been established and are supported by local parent groups. Their value in decreasing the need for additional institutional space is unquestioned and they will undoubtedly become an accepted and integral part of a publicly supported comprehensive program, if only for the economy involved.

Group III. This category of the mentally retarded includes those with the most profound degrees of intellectual handicap. This so-called low-grade group, with I.Q.'s of under 20 or 25, is fortunately the least common, and makes up 5 per cent or less of the

total problem. They can be recognized early in life with little difficulty, and there is an extremely high incidence of such associated handicaps as cerebral palsy and epilepsy which greatly increase the problem of home care. While many can be managed successfully in the community for limited periods during infancy and early childhood, continued home care presents a problem few families can long endure. Since the severity of the intellectual deficit makes it impossible to establish or develop any significantly satisfying interpersonal contacts, the mother-child relationship soon faces dangers that have important implications for the maintenance of a healthy family environment. It must be stressed, however, that the point in time when the separation of such a child from the family should take place is a highly personalized decision and the sole responsibility of the parents. For this decision to be reached for the best interests of all concerned, continued parental orientation and guidance are essential. Some type of residential care must eventually be supplied. In the past, the mortality rate for this group was so high that the need for long-term care, although always acute, was less pressing than is the case at present. Modern medical procedures have significantly increased the life span, and because of the highly personal nature of the care involved, the continued costs have become too great for all but the very few well-to-do to carry unaided. This is a humanitarian problem that must remain high on the list of public responsibilities.

In this country, as a rule, the problem of public residential care for this category of retardate has been met by the addition of nursery-like structures to our state training schools. Continual and unrealistic expansion of this type runs the risk of unduly diluting the administrative and supervisory interests from their important educational and training functions to the detriment of the over-all program. The needs of this group can be most effectively met by the establishment of small units of these nursery structures in the vicinity of larger centers of population. Much of the services required, such as medical care, are available and can be purchased on a local basis. Moreover, the supply of needed personnel that can be drawn from the enhanced potential employee pool that the larger cities afford will minimize one of the important problems. The reduced need for supplying personnel living quarters, so great an economic burden in the case of larger institutions in isolated areas, has important economic implications. The value of this type of decentralized residential care for maintaining the interest and enthusiasm of the parents, an important objective for the achievement and maintenance of the high standards of patient care, cannot be overemphasized.

Admittedly, this blueprint of a comprehensive program for the community care of the mentally retarded children will not be achieved in a short time for most of our country. Fortunately, it lends itself to stepwise progress, since the interrelationships of the various aspects are not mutually exclusive. For its eventual achievement, an enlightened public concern, a well-oriented parent group, as well as an interested, public spirited, and enthusiastic participation of our professional colleagues, are essential.

BRAZILIAN EXPERIENCE WITH ORAL B.C.G.

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BRAZIL was one of the few countries to adopt the oral method of administering B.C.G. (Moreau strain). Assis[1, 2] found it easy to use and without disagreeable side effects. With certain modifications in preparation and administration, the oral method proved to be as effective as the subcutaneous or intracutaneous methods. The key to success is the use of bacteria of high potency prepared from young cultures (ten days' maximum), and in large amounts (100 mg. in newborn infants, 200 mg. in older children). This method, besides being without danger, develops tuberculin positivity in from 70 to 97 per cent from the eighth to the sixteenth week, using intradermal tests up to 10 mg. of O.T.[3, 4] On the other hand, positive results as low as 30 or 40 per cent were recorded by investigators who used different types of vaccination (lower doses and older cultures) or less concentrated tuberculin tests before or after the period of maximum postvaccination allergy.[5-7] The morbidity and mortality from tuberculosis in babies intimately exposed to contamination and vaccinated with a single oral dose were 6.7 and 4.1 per cent, respectively, in contrast to 23.7 and 24.6 per cent in children not vaccinated and living under similar conditions.[8]

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The safety of the high B.C.G. dosage and its efficacy led the Brazilian researchers to seek a stronger form of immunization by means of a new technique: the administration of various doses of B.C.G., which they called "concorrent vaccination"* or "assisation," in honor of its inventor (Assis, 1945). This vaccination, as originally conceived by Assis,[9-12] consists in the administration, at monthly intervals, of six doses of 100 mg. for the newborn infant and 200 mg. for older children. It is particularly intended to protect children who are forced to live in a sputum-positive environment. A total of 4,655 infants thus vaccinated from birth were kept under observation for a period varying from two to eleven years. A tuberculosis morbidity of 2.06 per cent was recorded and the mortality was only 0.085 per cent[13] (Table I).

When the results obtained with the classical single-dose oral vaccination are compared with those of the concurrent vaccination and the nonvaccinated control, the great advantage of

*The word "concorrente" in Portugese has the same meaning as "concurrent" in English, i.e., "at the same time." This expression, "concurrent vaccination" ("vacinação concorrente"), was adopted originally by Assis in 1945 to designate a strong and rapid immunization by repeated oral B.C.G. of newborn infants who are unavoidably exposed to living with sputum-positive persons (meaning they "run together"). At present the expression is used in a broader sense and means intensive vaccination by repeated doses of B.C.G. of individuals at any age (newborn infants, older children, adults), whether they are or are not exposed to a sputum-positive focus.—*Editor's note.*

the concurrent method is noted (Table II).

Brazilian investigators have also used the concurrent B.C.G. method in allergic persons exposed to contagion. Rosemberg[8, 14, 15] and Silveira and Medeiros[16, 17] demonstrated the immunizing power of this method against the virulent reinfection (Table III).

really true, it is easy to imagine the possibilities of the concurrent oral B.C.G. vaccination, which can influence the allergy and the immunity produced by the virulent primary infection. This method is already being used not only as a prophylactic measure but also therapeutically. Good results have already been obtained

TABLE I. TUBERCULOSIS MORBIDITY AND MORTALITY AMONG 4,655 EXPOSED CHILDREN VACCINATED PERORALLY WITH SIX DOSES OF 100 MG. OF B.C.G.–MOREAU DURING THE FIRST SEMESTER AFTER BIRTH

	NUMBER OF CHILDREN	FOLLOW-UP (IN YEARS)	MORBIDITY		DEATHS	
			CASES	PER CENT	CASES	PER CENT
Center A*	1,207	2 to 11	27	2.23	0	—
Center B†	967	2 to 8	38	3.93	4	0.41
Center C‡	2,481	2 to 7	31	1.25	0	—
Total	4,655		96	2.06	4	0.085

*Dispensary of the Instituto Viscondessa de Moraes, Rio de Janeiro (A. de Assis). Tuberculosis exposure in individual homes.

†Dispensary N.S. Aparecida, Rio de Janeiro (E. Nascimento and A. Alvim). Multiple tuberculosis exposures in a slum district.

‡Dispensary of the Instituto Clemente Ferreira, São Paulo (J. Rosemberg). Tuberculosis exposure in individual homes.

TABLE II. TUBERCULOSIS MORBIDITY AND MORTALITY IN VACCINATED AND NONVACCINATED CHILDREN IN BRAZIL (PER CENT)

	CONTROL (NONVACCINATED)	ORAL B.C.G. (SINGLE DOSE)	ORAL B.C.G. (CONCURRENT)
Morbidity	23.7	6.7	2.06
Mortality	24.6	4.1	0.085

TABLE III. MORBIDITY AND MORTALITY OF TUBERCULOSIS IN VACCINATED AND NONVACCINATED ALLERGIC CHILDREN (PER CENT)

	ROSEMBERG		SILVEIRA AND MEDEIROS	
	208 VACCINATED	152 NOT VACCINATED	335 VACCINATED	287 NOT VACCINATED
Morbidity	0.96	4.9	1.49	4.88
Mortality	0	0.7	0	0.34

This apparent protective effect of the concurrent B.C.G. vaccination against tuberculous reinfection seems to be related to bacterial disallergization, as the repeated ingestion of B.C.G. has a desensitizing effect in allergic persons, especially the hypoallergic children, who may become completely negative to the Mantoux or even to infratuberculin tests. Repeated absorptions of the vaccine seem to *make more difficult the allergy in nonallergic organisms and to facilitate the desensitization in allergic organisms.* If this total independence or even antagonism between tuberculin hypersensitiveness and immunity is

with the concurrent vaccination in the treatment of hyperallergic cutaneous-mucous manifestations in infantile tuberculosis, consisting mainly of querato-conjunctivitis phlyctenularis, chronic rhinitis, eczema, intertrigo, and the condition classically known as scrofulosis.[18, 19]

The original method of Assis (six doses of 100 or 200 mg., at monthly intervals, totaling 600 to 1,200 mg.) has undergone various modifications, depending on individual investigators: fortnightly doses, weekly or even biweekly doses, and in totals varying

from 600 mg. to 4 Gm. of B.C.G. This method, officially recommended in Brazil for a contaminated focus, is beginning to be tried in other countries, particularly in Argentina, Tunisia, Czechoslovakia, and France.

(A) CONVERSION OF LEPROMIN TEST AFTER ORAL B.C.G. AND (B) PERSPECTIVE OF ANTILEPROSY IMMUNIZATION BY ORAL VACCINATION

The contribution of the Brazilian investigators had a great significance when it confirmed the converting power of the B.C.G. on the Mitsuda reaction (lepromine test), either in babies or in older children.[6, 7, 20-24] The systematic positivity of the Mitsuda in infants vaccinated with a single dose or repeated doses of oral B.C.G. has shown: (1) the adequate absorption of the vaccine by the digestive tract, which it had not yet been possible to prove by tuberculin tests, as these were frequently negative; (2) the reacting capacity of the reticuloendothelial system of the newborn infant to the antigenic stimulus of the vaccine, which had been doubtful previously.

The leprominic reaction induced by the oral vaccine appears between the twentieth and the sixtieth day after the vaccination, and seems to be permanent, contrary to the tuberculin reaction, which, as is well known, is temporary. The antigenic fraction of the tubercle bacillus, which is responsible for the leprominic reaction, may be identical to that existing in the Hansen bacillus and different from the antigenic fraction responsible for the tuberculin reaction.

In leprology a positive lepromin reaction is regarded as revealing a reacting state of the organism, which denotes an excellent condition of resistance in relation to infection by the leprosy bacillus. Therefore, studies are being conducted at present in Brazil in regard to the immunizing value of the Mitsuda test induced by B.C.G.

Souza Campos,[25] among 2,866 B.C.G.-vaccinated people who cohabitate with leprosy patients, found only sixteen cases of leprosy, all of the tuberculoid form, while among 6,141 nonvaccinated persons the incidence of leprosy amounted to 248 (sixty-two lepromatous, 115 undifferentiated, and seventy-one tuberculoid). The final answer, nevertheless, will depend on a decrease of endemic leprosy in the districts intensely vaccinated. At the present time various projects are being carried out in areas where leprosy is prevalent (Goyaz, Minas Geraes).

INDISCRIMINATE B.C.G. VACCINATION (WITHOUT PREVIOUS TUBERCULIN TESTS OR ROENTGENOGRAPHY)

In view of the proved safety of the B.C.G. both in the nonallergic and in the allergic, even where active tuberculous disease is present,[26, 27] the Brazilian school today recommends the vaccination of the population, without previous allergic tests or roentgenograms, in the same way as is done for the newborn infant. The oral vaccination (single or repeated doses) has proved to be extremely easy and permits mass campaigns against tuberculosis and leprosy, in large geographical areas where these diseases present a high epidemiological index.

SUMMARY

I am emphasizing the high protective value of the oral B.C.G. method used in Brazil, which is based particularly in (1) a special strain—Moreau; (2) young cultures; (3) high dosage

(100 to 200 mg.); (4) repeated doses, "concurrent vaccination" — monthly, fortnightly, weekly, or even bi-weekly, totaling 600 mg. to 4 Gm. Tuberculin positivity, produced by a a single dose of oral B.C.G. or by a previous virulent infection, becomes weaker or even negative, after repeated oral B.C.G. This tuberculin desensitization, according to the experience of Brazilian investigators, means, as a matter of fact, a bacterial disallergization, since it coincides with higher immunity. Lepromin-positive tests (Mitsuda), produced by a single dose of oral B.C.G., on the c o n t r a r y, become stronger when repeated doses are given. At present, studies are being conducted on the immunizing value of the positive lepromin test induced by B.C.G.

The Brazilian experience with oral B.C.G. has proved the safety of mass vaccination of the population, without previous tuberculin tests or roentgenograms, in the campaign against tuberculosis and, perhaps, leprosy.

REFERENCES

1. de Assis, A.: Diretrizes atuais da vacinação BCG no Brasil, Clinica Tisiológica **2**: 395, 1947.
2. de Assis, A.: Aspetos doutrinários e práticos da moderna orovacinação com BCG, Arch. di Tisiol. Mal. App. Resp. **10**: 563, 1955.
3. de Assis, A.: Alergia tuberculínica depois da vacinação oral do recém-nascido com dose única (100 mg.) de BCG, Hospital, Rio de Janeiro **33**: 169, 1948.
4. Rosemberg, J.: Die orale BCG Impfung beim Menschen, in Die BCG Schutzimpfung, by Prof. Rolf Griesbach of Augsburg, Stuttgart, Georg Thieme Verlag.
5. Budiansky, E.: Comportamento da alergia tuberculínica em filhos de leprosos após calmetização, Rev. brasil. de leprol. **17**: 28, 1949.
6. Budiansky, E., and Campos, E. C.: Papel do BCG na profilaxia da lepra, Rev. brasil. med. **10**: 258, 1953.
7. Budiansky, E., and Campos, E. C.: Comportamento das reações de Mantoux e Mitsuda em crianças calmetizadas por via oral (dose única e vacinação concorrente), II Congreso Internacional de Alergia, Nov., 1955, Rio de Janeiro.
8. Rosemberg, J.: Imunidade na Tuberculose, Rev. brasil. de tubere. **21**: 37, 1953.
9. de Assis, A.: Tolerancia do organismo adulto alérgico ao BCG, Hospital, Rio de Janeiro **28**: 875, 1945.
10. de Assis, A.: Vacinação BCG concorrente, Hospital, Rio de Janeiro **31**: 815, 1947.
11. de Assis, A.: Tuberculose domiciliar e vacinação BCG concorrente, Hospital, Rio de Janeiro **37**: 677, 1950.
12. de Assis, A.: Vaccination concomitante au BCG des nouveau nés et son influence sur la tuberculose infantile, Hospital, Rio de Janeiro **44**: 305, 1953.
13. de Assis, A.: Personal communication, 1956.
14. Rosemberg, J.: La vaccination par le B.C.G. chez les sujets allergiques, Rev. de la tubere. **14**: 490, 1950.
15. Rosemberg, J.: Resultados da vacinação BCG no Brasil, Rev. brasil. de tubere. **17**: 331, 1949.
16. da Silveira, J.: Poder protetor do BCG nos alérgicos, Tese, Faculdade de Medicina da Universidade da Bahia, 1949.
17. Silveira, J., and Medeiros, S.: Arq. Inst. Bras. Investig. Tubere. **12**: 6, 1953, Apud 2.
18. Budiansky, E.: BCG concorrente no tratamento de manifestações alérgicas de natureza tuberculosa (escrofulose), Comunicação áSociedade de Pediatria do Rio Grande do Sul, April, 1956.
19. Fernandes da Costa, A.: O poder dessensibilizante do BCG em oftalmologia, Tese, Faculdade de Medicina, Recife, 1953.
20. Pereira, P. C., and others: Imunidade induzida na lepra, Memoria del VI Congreso Internacional da Leprol., Madrid, 1953.
21. Rosemberg, J.: Campos, N. de S., and Aun, J. N.: Da relação imunobiológica entre tuberculose e lepra, Rev. brasil. de leprol. **18**: 3, 1950.
22. Rosemberg, J., Campos, N. de S., and Aun, J.: Estado atual do conhecimento da inversão da reação de Mitsuda por efeito do BCG oral, Hospital, Rio de Janeiro **44**: 33, 1953.
23. Salomão, A., and others: Imunidade induzida na lepra, Memoria del VI Congreso Internac. de Leprol., Madrid, 1953.
24. Souza Campos, N.: O BCG na profilaxia da lepra (Revisão bibliográfica), Rev. brasil. de leprol. **21**: 292, 1953.
25. Souza Campos, N.: Primeiros resultados do BCG na profilaxia da lepra, Memoria del Congreso Internac. de Leprol., Madrid, 1953.
26. Rosemberg, J.: Doutrina e prática da vacinação BCG indisgriminada, Rev. Paulista de Tisiologia **13**: 217, 1952.
27. Rosemberg, J.: Adminitração de BCG em doses intensivas a adultos portadores de Tb. pulmonar., Rev. brasil. de tubere. **22**: 211, 1954.

SUBACUTE SCLEROSING LEUKOENCEPHALITIS

VAN BOGAERT TYPE

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THE many degenerative diseases which affect the brain in children have for years been loosely grouped together and given the misleading name "diffuse encephalopathy." Various writers, however, have focused attention on the fact that certain disease entities could be clearly distinguished both clinically and pathologically, and predicted that an orderly classification of all the encephalopathies of childhood would eventually be established.

One of us (C. M. P.), in collaboration with Dr. Ludo van Bogaert, has recently reviewed the question of classification of the numerous maladies commonly grouped under the all-too-inclusive term "Schilder's disease."

Aside from the perinatal anoxic or traumatic encephalopathies, the first group to be identified was that established by Schilder in 1912: encephalitis periaxialis diffusa. Schilder himself actually wrote about three different entities in his three original case reports published in 1912, 1913, and 1924. The 1912 case has generally been accepted as the prototype of the diffuse type of primary demyelinating disease, which may be a variant form of multiple sclerosis, while the 1913 case deals with an instance of a familial type of demyelinating disease now called leukodystrophy which is closely related to the lipidoses. In his 1924 paper, Schilder described in detail a process characterized by extensive demyelinization, with strong evidence of an inflammatory component. Lumsden was the first to point out that this case belonged to the group of subacute encephalitides.

A specific type of subacute encephalitis was delineated in Europe in 1939 by van Bogaert and De Busscher in an article entitled "Inflammatory Sclerosis of the Spielmeyer Type." In 1945, van Bogaert published five case reports of this entity with anatomical confirmation and called the process "subacute sclerosing leucoencephalitis." The clinical picture of this disease, which occurred exclusively in children, consisted of early intellectual deterioration with rapid and severe involvement of all the higher functions, various types of dyskinesias ranging from myoclonic jerks to convulsive episodes, and a subacute course leading to bilateral spasticity, decerebrate rigidity, cachexia, dementia, and death. This clinical course proved to be typical enough to permit premortem diagnosis. The pathologic features in all these cases were also found to be pathognomonic, and therefore on the basis of both clinical and

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pathologic features van Bogaert felt that the disease deserved a special place in the nosology of the encephalitides. In 1949, Radermecker outlined characteristic changes in the electroencephalographic tracings in these cases. These changes have since proved to be a valuable adjunct in making the diagnosis of this condition.

It is our purpose in presenting these case reports to demonstrate the characteristic clinical, pathologic, and electroencephalographic features of van Bogaert's subacute sclerosing leukoencephalitis.

CASE REPORTS

CASE 1.—D. P., a 6-year-old white male. The disease had its onset with vomiting, slight temperature, and lower abdominal pain. After an appendectomy was performed the symptoms continued and the child was irritable, easily fatigued, lost weight, and became indifferent to his surroundings. His scholastic ability began to diminish rapidly, and his parents noticed that he had an intention tremor with sudden tonic or pseudochoreic movements, in particular on the right side of his body.

By the third month of the illness, the child had deteriorated to almost complete dementia. He could hardly say his own name and exhibited a severe nominal aphasia, as well as some receptive difficulty, but he did obey simple commands. Neurological examination at that time showed a masked facies, plastic hypertonicity and spasticity of the right limbs. There were many abnormal movements on the left side of the body with isolated myoclonic jerks in almost all muscle groups, including the face and abdomen, and occasional ballic motions of the left arm. Generalized clonic movements of the entire body occurred almost rhythmically at a rate of about fifteen to twenty per minute. Between these generalized movements, there were also athetoid movements of the limbs. The intensity and frequency of the dyskinesias varied considerably. The child deteriorated quickly and died three months after the onset of the disease.

The laboratory tests were unremarkable. The cerebrospinal fluid showed 1 cell and protein of 40 mg. per cent. (The pathologic findings will be discussed in a separate section.)

CASE 2.—S. D., 12-year-old white female. The disease started with an episode of nausea and vomiting which was followed the next day by a period during which the child dropped whatever she held in her hand. She spoke in jargon. She had a generalized convulsive seizure which was followed by right hemiparesis and coma lasting three hours. She then improved over a period of several days. The next month there was slow development of left hemiparesis associated with involuntary myoclonic movements of the left side of the face. The child became more apathetic, spoke little, and showed defects of memory. She complained of painful leg muscle spasms.

At the end of the second month of her illness, the patient had a mild right hemiparesis with athetotic posturing, a left hemiparesis, monosyllabic speech, a short attention span, and frequent eye blinking accompanied by ticlike myoclonic jerks of the left side of the face. There were also nonrhythmic clonic movements of the left arm which occasionally also involved the opposite limbs. The patient had become quite dull mentally. At this time she had an unexplained fever reaching 103° F., after which she became deeply stuporous, incontinent, and unresponsive, with trismus, flaccidity of the left side, and bilateral extensor plantar responses. After two or three days the child improved but continued to have generalized flexor spasms every fifteen or twenty seconds. The least tactile or auditory stimulus would result in a spell of spasmodic crying and periods of apnea.

A couple of weeks later the patient had two more generalized convulsions

followed by coma. She never recovered consciousness after this, remaining in a decerebrate attitude with episodes of spasmodic crying and elevation of the right arm and rotation of the head to the left. She had several periods of unexplained fever and died during one of them seven and one-half months after the illness began.

Throughout the course of the disease, laboratory tests were within normal limits, the cerebrospinal fluid showing 2 cells, a protein of 41 mg. per cent, and a first-zone Lange curve. (Pathologic findings will be discussed in a separate section.)

CASE 3.—R. H., 10-year-old white male. The disease started with a series of right-sided focal clonic seizures occurring two or three times a day. After a week had passed the child suffered from a sudden attack of acute anxiety with hallucinosis, severe agitation, and at least one suicidal gesture. This state lasted about four hours. Two days later a right hemiparesis set in, and thereafter the child's vocabulary became restricted and he appeared less mature than before. Within a few weeks the right hemiparesis progressed and soon walking became impossible because of superimposed severe trunkal ataxia. Convulsive episodes grew more frequent. By the middle of the second month of illness the child had lost his speech almost completely and exhibited almost constant clonic movements of all extremities. Several weeks later speech and voluntary motion were gone.

Neurological examination revealed an almost comatose cachetic child with full right hemiplegia. There were occasional upward movements of the eyes and hands. The neck was stiff, and there were bilateral papilledema and complete areflexia. A few days later the coma seemed less deep. Reflexes were again obtainable and there were brief lapses of consciousness. The child apparently was still able to hear and see. He had sudden short episodes of perspiration and facial redness. He died a few weeks later during an unexplained fever.

The laboratory examinations were unremarkable. The cerebrospinal fluid showed 1 cell, a total protein of 38 mg. per cent, and a first-zone Lange curve. The duration of the illness was about four months. (Pathologic findings will be discussed in a separate section.)

CASE 4.—J. D., 6-year-old white female. The child's teacher was the first to note that she had rather suddenly begun to show lessened aptitude, and was more awkward and less attentive in class. Then frequent akinetic seizures manifested themselves. The child's personality changed: she was quieter, she refused to eat by herself, and she had night terrors. Stereotyped involuntary movements in the form of "salaam ties" appeared, mainly at night. A few weeks after the onset of the disease she had her first grand mal convulsion.

The patient was examined and found to be deteriorated mentally. She had frequent involuntary movements which at times were ticlike but at others consisted of suddenly turning the head to the right while raising the left arm. There was a mild right hemiparesis with right facial weakness, but deep tendon reflexes were equal and the plantar responses remained flexor. The optic fundi were normal. The cerebrospinal fluid showed 5 cells, a total protein of 32 mg. per cent with a positive Pandy, and a slight first-zone Lange curve. The child was lost to follow-up and no further details are known about the course of her disease.

CASE 5.—J. V., 7-year-old white female. The first symptoms of illness consisted of deterioration in the child's table manners. About two months afterward she started having brief lapses of attention, she became indifferent to her surroundings, and her affect seemed diminished. A month later she suddenly became ataxic and fell, and bilateral leg spasticity set in. During the next three months she

had two grand mal seizures. Her mental status was variable; on some days she appeared normal, while on others she was depressed and quiet. Her school work had already suffered considerably and there was evidence of advanced intellectual impairment. She had become progressively more somnolent and irritable and fatigued easily.

The child's face was expressionless and fixed. She had periods of inappropriate laughter. No dyskinesias were noted except for an occasional eye blink which was associated with slight facial relaxation and general loss of muscle tone. Her hands, when held extended, assumed an athetoid posture. Occasionally salutatory tic-like movements of the trunk were observed during sleep. Fine movements were uncoordinated, and she had a fine tremor of the upper extremities. Her tongue deviated slightly to the right.

The child was lost to follow-up, and no further details are known about the course of her disease.

CASE 6.—L. B., 7-year-old white male. The disease started with gait difficulties caused by many unexplained falls. Then the child had short lapses of consciousness. He had a rapid loss of scholastic ability, resulting from severe intellectual impairment. He became bedridden after a few weeks, and often had generalized clonic seizures. Two months after the onset of the illness he had quadriparesis with a superimposed extrapyramidal component. There were frequent periods of unexplained high temperature.

At this time the cerebrospinal fluid showed 1 cell, with a total protein of 22 mg. per cent. A pneumoencephalogram is reported to have revealed large ventricles without shift or deformity. On psychologic examination the child was found to be functioning at the level of a 4½-year-old with loss of attention and difficulty in concentration. A month later he had deteriorated even further. He was disoriented, but he attempted to carry out simple commands. His speech was impeded by frequent clonic movements, tremulous, dysarthric, and almost unintelligible. There were echolalia and perseveration. The facies was expressionless and the body was held in a decerebrate attitude with legs in extension and arms in flexion. He had rhythmic movements of all extremities, with occasional isolated myoclonic jerks of face, abdomen, and limbs. His deep-tendon reflexes were equal and active and the plantar responses were equivocal. The optic fundi were normal. A re-examination of the cerebrospinal fluid showed 1 cell, total protein of 17 mg. per cent, a negative Pandy, and a first-zone Lange curve.

The child was lost to follow-up, and no further details are known about the course of his disease.

CASE 7.—K. F., 8-year-old white female. The disease started with frequent episodes during which the child's head dropped for a few seconds. Shortly thereafter she became ataxic and had occasional falls. Her school work grew poorer. Anti-convulsant drugs were ineffective, her ataxia increased, and she began to drop objects frequently. Her muscular coordination was impaired. She exhibited frequent pseudovoluntary movements of the hands, showed signs of intellectual deterioration, and had periods of inappropriate laughing and crying. She could no longer participate in conversation.

Neurological examination revealed dilated pupils which reacted sluggishly to light. The child was hyperkinetic and agitated, and made many choreiform movements. Her speech was incoherent. She walked with a wide-based gait and fell to the right. There were dysmetria, slight weakness of the left arm, and a left Babinski sign. Four months after the disease began, the child had become drowsy; her speech was thick, and there was some dysphagia. She cried almost continuously. Deep-tendon reflexes were hypoactive. Laboratory examinations were all normal. The cerebrospinal

fluid showed 2 cells, and there was a total protein of 59 mg. per cent and a first-zone Lange curve. A pneumoencephalogram revealed slight ventricular dilatation without shift or deformity. The child died nine or ten months following the onset of the disease. An autopsy was not obtained.

COMMENT

All the children had entirely negative past histories. Their development had been completely normal and no sibling was affected by a similar disease. Such family histories as could be obtained revealed no neurological or mental disease except in Case 7, in which two siblings had a convulsive disorder classified as petit mal. All the children had routine laboratory studies of blood and urine. Chest and skull x-rays were negative. The serology was negative in both blood and cerebrospinal fluid in all cases.

Electroencephalographic tracings were obtained in all seven cases. In many, serial tracings were taken. In all seven cases, the abnormal rhythmic complexes were seen in electroencephalograms on at least one occasion, and in several cases these occurred consistently in all tracings. Representative electroencephalograms from three cases (3, 4, and 7) illustrating the characteristic complexes and their variations from day to day can be seen in Figs. 10 through 18.

Even though only three of the seven cases were confirmed at autopsy, the clinical histories and electroencephalographic tracings were deemed sufficiently typical to warrant the diagnosis of subacute sclerosing leukoencephalitis.

PATHOLOGIC EXAMINATIONS OF THREE CASES

CASE 1 (D. P.).—On microscopic examination a section of the brain revealed diffuse involvement and grayish discoloration of the cerebral white matter.

Microscopic sections stained with myelin sheath stain showed diffuse bilateral involvement of the entire cerebral centrum ovale. The white matter appeared gray instead of the usual black. This discoloration was uniform throughout the lesion and

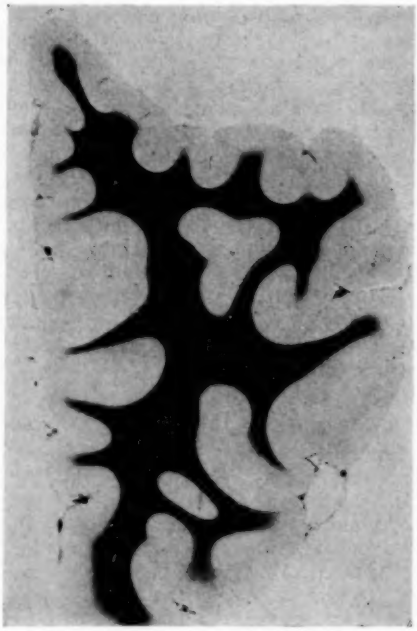

Fig. 1.—Section through frontal pole; note the minimal degree of demyelinization with moth-eaten appearance. Case 1. (Celloidin, Woelcke.)

gave a moth-eaten or threadbare appearance (Fig. 1). The demyelinization extended centrally to involve the thalamus and the corpus Luysi. The same type of demyelinization pervaded the convolutions of the paracentral lobule, the parietal lobe, and the medial and inferior temporal region. The cerebellar, pontine, and medullary myelin appeared intact but definite involvements of the spinocerebellar tracts and of the fasciculi of Helwig and Goll were noted in the cervical spinal cord.

The Holzer stain showed an extensive, diffuse, isomorphic fibrillary gliosis of the anterior centrum ovale, and the paracentral, parietal, and anterior temporal regions (Fig. 2). The optic radiations and the subcortical fibers of the calcarine regions were equally involved. The gliotic process affected

Fig. 2.—Same section as in Fig. 1, demonstrating severe, diffuse gliosis of entire white matter with scattered glial nodules. Case 1. (Celloidin, Holzer.)

the hilar cerebellar structures and the medullary olives. There was a marked disparity between the severity of the gliosis and the rather moderate degree of demyelinization in all those areas. Fat stains showed considerable quantities of neutral fat, both lying free in the parenchyma and contained in macrophages. These fatty products of degeneration were found in dense masses in the subcortical white matter of the calcarine region, and in the temporal convolutions. They were completely lacking in the paracentral lobule, the parietal convolutions, and the cuneus. In some areas, fixed glial cells also contained some fatty material.

The Nissl stain showed the frontal cortex architecture to be well preserved, but there were disseminated discrete glial nodules, especially in layers II and III, as well as some perivascular round-cell infiltrates. Similar glial nodules and perivascular cuffs were found throughout the subcortical white matter.

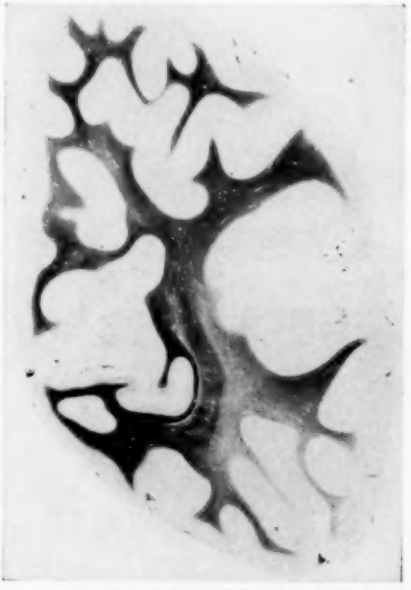

Fig. 3.—Section through occipital lobe and calcarine region, showing varying degree of demyelinization. Case 1. (Celloidin, Woelcke.)

The histologic picture was similar for the temporal, parietal, and occipital lobes (Fig. 3). The meninges showed perivascular cuffs. The hippocampus was moderately involved, while the amygdaloid nucleus was almost completely replaced by gliosis. The mammillary bodies and the substantia nigra were less severely affected, but there was appreciable gliosis of the corpus Luysi.

The thalamus exhibited extensive cellular losses especially involving the

dorsolateral and ventrolateral nuclei. Most of the large cells of the globus pallidus had disappeared, while the putamen and caudate nucleus were intact. The claustrum and insular cortex showed advanced lesions. The hypothalamic structures, such as the tuber cinereum and the supraoptic nucleus, were affected. The lesions consisted of cellular loss, gliosis, and perivascular cuffing. In the cerebellum, the dentate nucleus showed some cellular rarefaction. There were a few glial nodules in the cerebellar cortex and the axes of the lamellae. The blood vessels of the cerebellar hilum were distended, and there was plasma exudation and intra- and extra-adventitial infiltration with lymphocytes and plasma cells. The ventral nuclei of the pons, the trigeminal root, and the olives were all involved to varying degrees.

The lesions in the spinal cord consisted of a periependymal gliosis and a diffuse gliosis of the anterior and intermediolateral horns and of the posterior columns. These lesions were most pronounced in the cervical region and were absent below. The spinal ganglia suffered cellular loss, gliosis, and perivascular cuffing. The preganglionic dorsal root was intact, but the postganglionic portion of the root

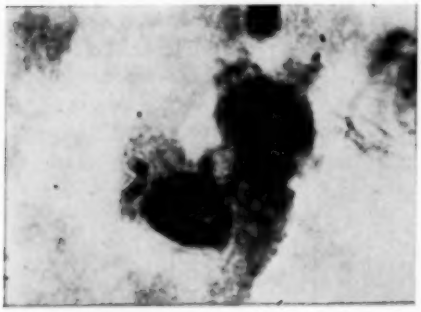

Fig. 4.—Glial cell with homogeneous eosinophilic intracytoplasmic inclusion body in hippocampus. Case 1. (Paraffin, H & E.)

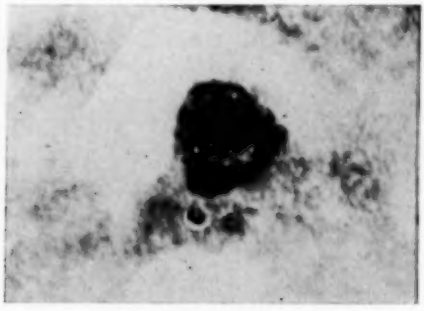

Fig. 5.—Glial cell containing two intracytoplasmic inclusion bodies of different densities with granular texture in hippocampus. Case 1. (Paraffin, H & E.)

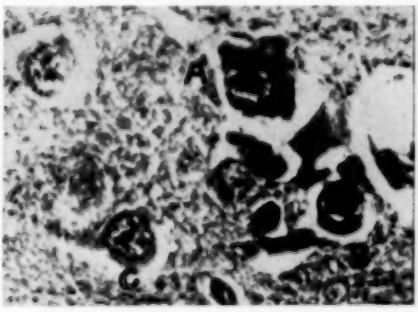

Fig. 6.—*A* and *B*, Two glial cells containing both intranuclear and intracytoplasmic inclusion bodies. In both cells the inclusion body in the nucleus is surrounded by a distinct halo. In *C* a single comma-shaped inclusion body can be seen in the nucleus. Paracentral cortex. Case 2. (Paraffin, H. & E.)

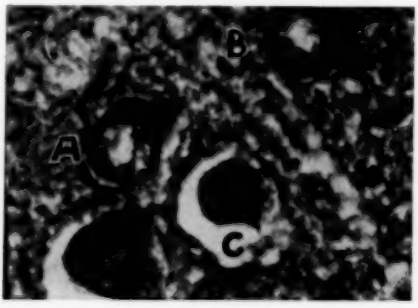

Fig. 7.—*A* and *B*, The nucleus of both glial cells is vacuolized. This change seems to be a precursor to the presence of intranuclear inclusion material. *C*, Multiple, punctate eosinophilic inclusion material in the cytoplasm of a glial cell. Paracentral cortex. Case 2. (Paraffin, H & E.)

exhibited some perivascular infiltrates. The peripheral nerves were intact. The optic chiasm showed diffuse round-cell and plasma-cell infiltrates and edema of the intracranial portion of the optic nerves.

A diligent search for inclusion bodies on sections stained with hematoxylin and eosin revealed intracytoplasmic inclusion in only two glial cells of the hippocampus (Figs. 4 and 5).

volution. The parietoangular and temporal lesions were more evident posteriorly. The thalamus was severely affected in its ventrolateral, centromedian, and medial nuclei. The cerebellum was little involved, as were the globus pallidus, the substantia nigra, the corpus striatum, the corpus Luysi, and the hypothalamus. There were scattered small lesions in the medulla and the spinal cord.

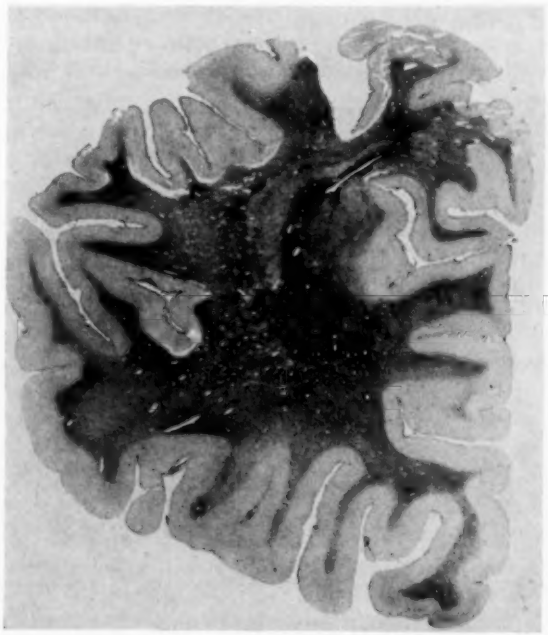

Fig. 8.—Section through the calcarine region demonstrating severe gliosis of the entire white matter. Case 3. (Frozen, Holzer.)

CASE 2 (S. D.).—The involvement was identical in type and structure to that described above, but the topography of the lesions differed slightly. The most important lesions were found bilaterally in the orbital region of the frontal lobe, and involved the convexity of the second and third frontal convolutions and the cingulate gyrus. The angular gyrus was greatly affected, as were the second and third temporal convolutions and the inferior surface of the first temporal convolution.

Numerous intranuclear and intracytoplasmic inclusion bodies were found in glial cells in the superficial cortex of the paracentral lobule (Figs. 6 and 7).

CASE 3 (R. H).—The same pathologic process, consisting of demyelinization, cellular losses, gliosis which was both diffuse and nodular, and perivascular infiltrations made up of lymphocytes and plasma cells, was found in the microscopic examination of this brain. Sections stained with

Scharlach again revealed a dense accumulation of neutral fat in the parenchyma, as well as contained in macrophages, and corresponding to the distribution of gliosis (Figs. 8 and 9). The lesions involved the frontal, motor, and occipital cortex and their subcortical white matter; the claustrum; the thalamus, especially the anterior and medial nuclei; the putamen; the globus pallidus; and the substantia nigra. Lesions were conspicuous in the substantia nigra. The cerebellar roof nuclei showed widespread cellular losses less marked in the dentate nuclei and in the folia. Many glial nodules were found in the reticular substance and the ventral nuclei of the pons, as well as in the nuclei of Goll and Burdach and of the vagus in the medulla. Glial nodules were also present in the cervical cord in the periependymal region and the posterior and lateral columns. No inclusion bodies were found in any of the numerous sections searched. An incidental finding was the presence of cervical syringomyelia.

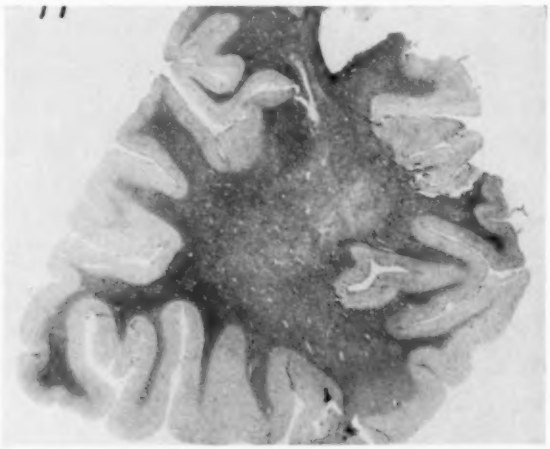

Fig. 9.—Same section as in Fig. 8, showing densely packed, fat-laden macrophages occupying all but the center of the subcortical white matter. Case 3. (Frozen, Scharlach.)

DISCUSSION

Clinical Aspects.—Subacute sclerosing leukoencephalitis, the name given to the disease in these cases, indicates its subacute course, the fact that it is the white matter of the brain that is principally affected, and that the basic process is one of inflammatory sclerosis or gliosis.

The clinical picture consists of the following features: the disease affects children or young adolescents; it progresses in a subacute fashion and is fatal after a course usually lasting several months; there is early intellectual deterioration with rapid and severe involvement of all psychic functions, usually encompassing some element of agnosia, apraxia, or aphasia, leading to eventual complete dementia; diminution of scholastic ability is a common and prominent early symptom. There are convulsive episodes which are frequently associated with complex dyskinesias and hyperkinesias of various types, such as clonic discharges, pseudochoreic movements, ballism, myoclonic jerks, tonic fits with opisthotonos or dystonic manifestations. The course of the disease leads

to bilateral spasticity and eventually to decerebrate rigidity. The pyramidal tract signs are inconstant, however. Usually the patient becomes cachectic and has frequent unexplained periods of fever. Blood, urine, and spinal fluid examinations are almost always within normal limits except that the spinal fluid colloidal gold curve is frequently of the paralytic type.

The disease habitually progresses without remissions, and its course may be roughly divided into three stages according to the symptom complex dominant at the time; psychic and intellectual deterioration usually comes first and is then followed by a period during which various dyskinesias and neurological signs are exhibited. The third stage consists of decerebrate rigidity and complete dementia.

No predisposing factors or prodromal symptoms have so far been recognized; nor has there been any evidence pointing to a seasonal or geographic predilection.

Histopathologic Aspects.—The histopathologic picture is almost as characteristic as is the clinical syndrome. It consists of fibrillary gliosis, which is believed to be the main pathologic process, accompanied by a subacute inflammatory reaction largely evidenced by lymphocytes and plasma cells. This reaction extends diffusely throughout the entire white matter, but at times spills over considerably into the cortex, the basal ganglia, and the thalamus. The myelin sheaths may be moderately or minimally involved although the fibrillary gliosis is active. The lesions are usually most severe in the subcortical white matter and diminish in intensity caudally, although lesions are often found in the cord and the spinal roots and rarely in the peripheral nerves. The demyelinization is probably a secondary response and the remarkable degree of gliosis in areas showing little or no demyelinization is one of the characteristic features of this disease process.

Sections stained for myelin sheaths often have a moth-eaten, threadbare appearance, although they may look normal. The gliosis is isomorphic; the axones may or may not be involved, depending upon the severity of the process. The catabolism of myelin is carried out actively by the microglia to the stage of neutral fats. Scattered throughout the nervous system are characteristic glial nodules involving the cortex, as well as the gray matter, and nuclear formations, as well as tracts. Perivascular cuffs consisting of lymphocytes and plasma cells are found throughout in white and gray matter and the meninges, varying in intensity and presenting evidence of an inflammatory reaction. Cellular losses in various nuclei are frequently encountered, especially in the region of the basal ganglia and of the thalamus.

Inclusion bodies have been found in certain cases of this disease. Because of this several investigators have been prompted to pursue viral studies, but no results have so far been published. The earliest reports of the disease made no reference to inclusion bodies. Martin and associates, in 1950, were the first to mention such findings. The original material in the laboratory of the Institut Bunge was then re-examined and such inclusion bodies were indeed found in one of the cases which had been published by Dubois and coworkers in 1949. Geinert and Müller,

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in 1955, reported another case of subacute sclerosing leukoencephalitis with inclusion bodies. Two of the three cases discussed in this paper which were examined post mortem contained inclusion bodies. In Case 1, only 2 cells were found with intracytoplasmic inclusion bodies, while in Case 2 there were numerous cells with both intranuclear and intracytoplasmic inclusion bodies.

The pathologic aspects are typical enough, when coupled with the clinical syndrome, to allow for definitive diagnosis to be made by cerebral biopsy.[3]

Electroencephalographic Aspects.—The characteristic electroencephalographic pattern may give a valuable clue to the correct pre-mortem diagnosis of this condition.

To date electroencephalograms have been performed serially on twenty patients in whom the clinical course and the electroencephalographic pattern have allowed us to make the diagnosis of subacute sclerosing leukoencephalitis. Post-mortem examination performed on twelve of those patients confirmed the diagnosis. In at least two cases the electroencephalographic

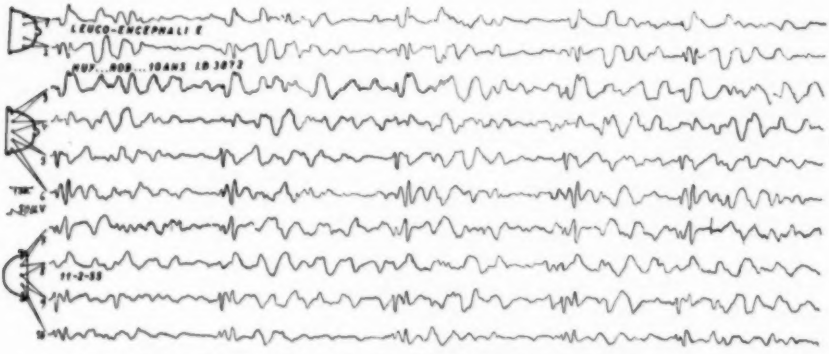

Fig. 10.—Electroencephalogram on Feb. 11, 1955. Diffusely abnormal with bursts of high-voltage slow waves appearing paroxysmally bilaterally with a frequency of seven to eight per minute. Case 3.

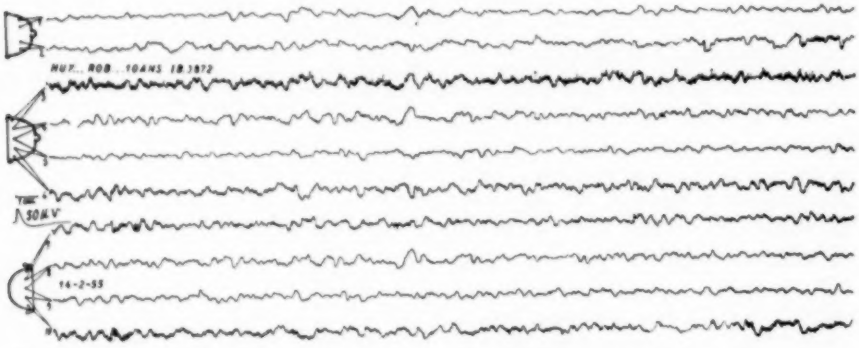

Fig. 11.—Electroencephalogram on Feb. 14, 1955. The abnormal bursts are less regular, and difficult to pick out. Tracing is nonspecific. Case 3.

pattern indicated the correct diagnosis before the clinical picture was sufficiently well developed to do so.

The first recordings by one of us (J. R.) in such cases in 1948 (published 1949) showed paroxysmal high-voltage complexes, initiated by the appearance of one or more spike waves, superimposed upon a basic rhythm which grew slower and slower and finally became completely disorganized. The spike waves appeared to be synchronous with myoclonic jerks that could be observed clinically.

These rhythmic complexes start most often with one or a few slow spike discharges which may consist of only a slight departure from the base line or even of a slight notch on the ascending limb of the first slow wave. The second part of the complex is a train of high-voltage slow waves varying in amplitude from 200 to 400 microvolts. These slow waves may resemble a deformed "K" complex or simply be composed of a train of waves of decreasing amplitude lasting for one or two seconds. The rhythm is strikingly

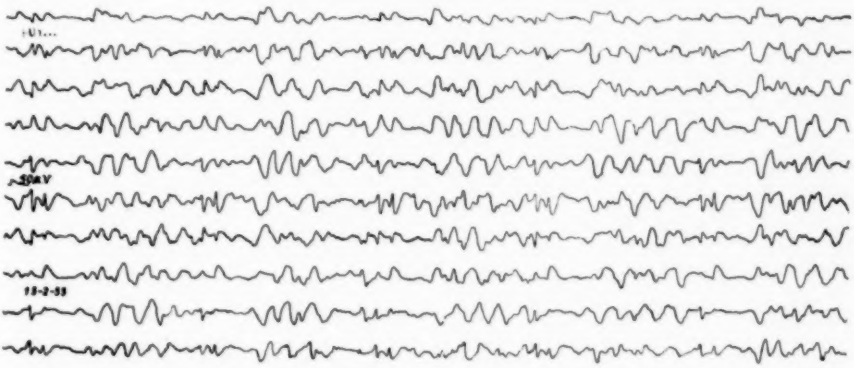

Fig. 12.—Electroencephalogram on Feb. 15, 1955. Tracing is similar to that obtained on February 11, but the complexes are not as typical. (Electrode placement as in Fig. 11.) Case 3.

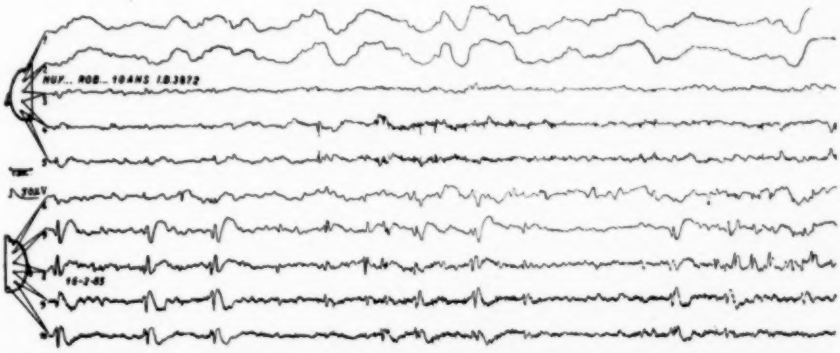

Fig. 13.—Electroencephalogram on Feb. 16, 1955. Tracing is quite asymmetrical. The paroxysmal bursts appear only on the right side and there seems to be little rhythmicity to their appearance. There is depression of electrical activity over the left hemisphere. Case 3.

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regular, at least during the same tracing, and has a frequency varying between two to four and sixteen to eighteen per minute, with a mean of six to eight per minute. The complexes appear synchronously in all leads but are preponderantly frontocentral. The complexes are isomorphic in the same lead during the same recording, although the shape may differ from one lead to another and from one tracing to another. They are not always present in each case, and no correlation has been established between their appearance in the tracing and the clinical course of the disease. Daily changes in the electroencephalographic recordings are illustrated in Cases 3 and 4 (Figs. 10 to 17). It can be clearly seen that the characteristic complexes may be missed if only a single tracing is obtained.

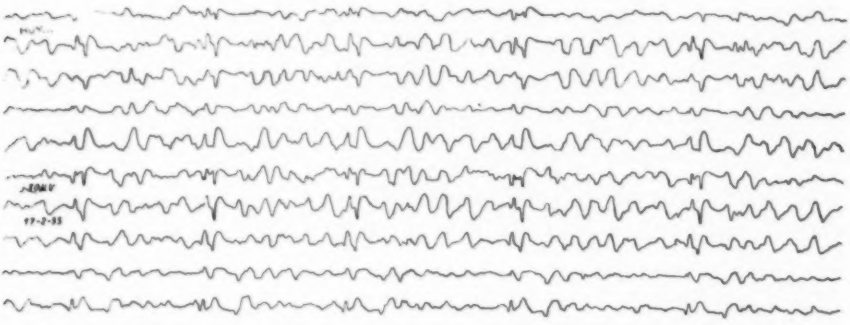

Fig. 14.—Electroencephalogram on Feb. 17, 1955. Generalized slowing bilaterally. Electrical depression on the left has disappeared. There are bilateral discharges occurring at a rate of seven to eight per minute and consisting of a biphasic spikelike wave followed by high-voltage slow waves. (Electrode placement as in Fig. 13.) Case 3.

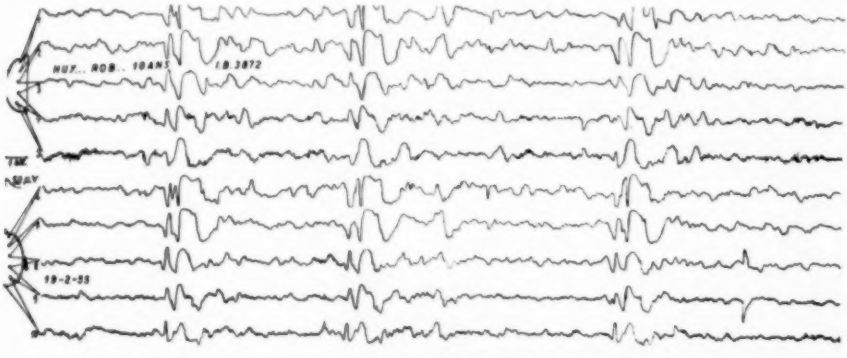

Fig. 15.—Electroencephalogram on Feb. 19, 1955. The paroxysmal complexes are still present bilaterally but they appear less frequently and there is a slight lag on the right side. Case 3.

In reviewing the available literature on electroencephalography and encephalitis, we noted similar complexes in a case reported by Balthasar in 1944 as an instance of nodular panencephalitis of the Pette-Döring type. At the International Congress of Neurology in Paris in 1949, Cobb and

Hill[7] presented electroencephalographic tracings identical to those reported in cases of subacute sclerosing leukoencephalitis, which they had obtained from patients whose disease had been diagnosed as inclusion-body encephalitis of the Dawson type. Foley and Williams[11] subsequently reported similar tracings in cases of inclusion-body encephalitis and subacute sclerosing leukoencephalitis. The characteristic electroencephalographic tracings in subacute sclerosing leukoencephalitis have since been reported from many laboratories in western Europe.

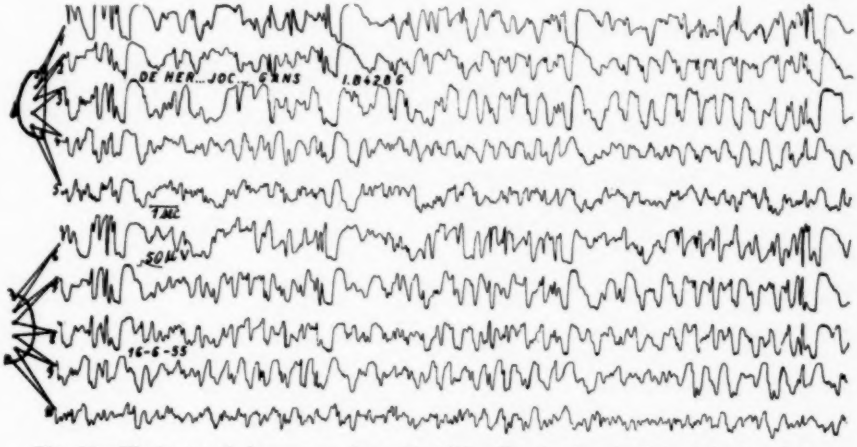

Fig. 16.—Electroencephalogram on June 16, 1955. The tracing is disorganized and dominated by high-voltage slow waves frequently associated with spikes. Complexes consisting of one or two spikes followed by trains of high-voltage slow waves of decreasing amplitude appear with a frequency of about eight per minute. Case 4.

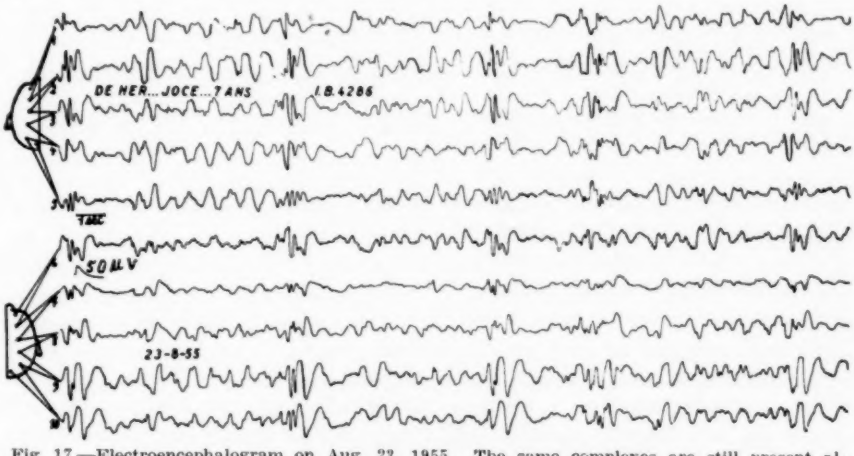

Fig. 17.—Electroencephalogram on Aug. 23, 1955. The same complexes are still present although the slow-wave component is less remarkable. Case 4.

Two reports of the electroencephalographic findings in cases of subacute

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sclerosing leukoencephalitis were published in the United States: Akelaitis and Zeldis[1] and Landau and Gitt,[14] and one in Canada, Van Buren.[20] The first report contained only one tracing, which was recorded about a month after the onset of the disease. It consisted of large slow waves; no paroxysmal rhythmic discharges were mentioned. In the second publication the fragments of tracing are so small that since the report mentions only "a slow paroxysmal dysrhythmia with a tendency to occipital foci," it is difficult to decide if these findings really correspond to what we have observed. But there is no doubt that the case reported by Van Buren is identical in all respects—clinically, pathologically, and electroencephalographically—with the classical picture of subacute sclerosing leukoencephalitis. Recently Lesse and associates[15] presented a series of electroencephalographic tracings obtained in a variety of conditions, including one proved case of subacute inclusion-body encephalitis, which have in common a certain rhythmicity of paroxysmal slow-wave discharges. Except for the case of inclusion-body encephalitis, in which the complexes are typical, the paroxysmal discharges do not correspond morphologically to those described above. Their report focuses attention upon the phenomenon of nonconvulsive rhythmic discharges and may lead to a re-evaluation of our concepts concerning the origin of such electrical activity in different conditions. In our personal experience, this typical electroencephalographic pattern has not been encountered in conditions other than subacute sclerosing leukoencephalitis.

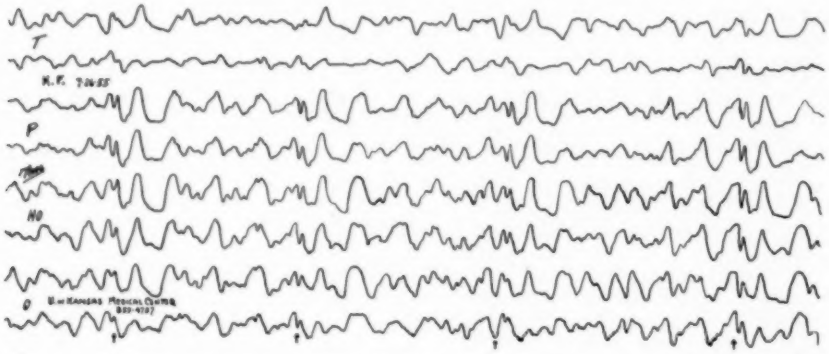

Fig. 18.—Electroencephalogram on July 26, 1955. Typical complexes consisting of a spike-like discharge followed by several high-voltage slow waves of decreasing amplitude. These occur with a frequency of about twelve per minute. Case 7.

Attempts have been made to explain the appearance of the complexes on the basis of the accompanying myoclonic jerks. Simultaneous recordings of the electroencephalogram and the electromyogram by Martin and colleagues[19] indicated that the electroencephalographic complexes were synchronous with the electromyographic discharges. However, the electroencephalographic complexes were still present during sleep, when the myoclonic jerks had disappeared. It has

also been shown that the electromyographic potential of the muscular discharge, almost always from arm muscles, occasionally precedes the electroencephalographic complex with a latent period as short as 1/10 second. These time factors, along with the morphologic identity of the EEG complexes (in spite of the fact that the myoclonic jerks might arise in any part of the body and be either discrete or diffuse) seem proof enough that the cortical complexes are neither the cause of the myoclonic jerks nor their result.

It has been suggested[22] that the complexes and the hyperkinetic muscular discharges might both be the result of the same subcortical pacemaker. From the clinical and pathological findings in this condition, it is possible to infer that lesions involving the reticular formation of the meseneephalon and its connections with the hypothalamus and thalamus markedly affect the function of the so-called waking center in a manner analogous to physiologic or barbiturate sleep and in doing so liberate dieneephalic-cortical neuronal automatisms. The epileptiform discharges resulting from the irritative character of the lesion then may well be transformed into a rhythmic pattern by the periodicity of the thalamocortical system. These discharges would have descending and ascending components, the former activating bulbospinal motor centers which result in diffuse myoclonic jerks, the latter being responsible for the cortical complexes. The fast component of the cortical complex, synchronous with the myoclonic jerk, would then represent the direct ascending part of the epileptiform discharge, while the slow waves, similar to the "K" complex, would be interpreted as a secondary discharge following the spike from the same irritative focus. The morphologic variation of the complexes from day to day would reflect the variable degree of functional and anatomic disturbance of the cortex and subcortical structures.

An interesting analysis of the electroencephalogram in a case of inclusion-body encephalitis was published by Campbell and associates.[6]

Nosological Aspects.—Case reports of ill-defined, atypical encephalitides began to appear in the literature after the disappearance of the great epidemics of encephalitis of the late 1910's and early 1920's. Dawson's report in 1934 brought attention to a peculiar finding in what he called a case of epidemic encephalitis of von Economo. In 1939, the year of van Bogaert and De Busscher's first report of subacute sclerosing leukoencephalitis, Pette and Döring[20] published a case of what they termed nodular panencephalitis. The pathologic findings were strongly reminiscent of the Japanese B type of encephalitis, a disease which had never been found in western Europe. Even though the clinical picture was quite similar to that seen in subacute sclerosing leukoencephalitis, the disease process involved the gray matter rather than the white.

Brain and co-workers,[5] and Malamud and associates[18] described series of cases of varied clinical and pathologic aspects in which the remarkable feature was the presence of intranuclear and intracytoplasmic inclusion bodies of the kind previously described by Dawson. Both an acute and a subacute form can be recognized, the latter having undeniable clinical and

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pathologic similarity to subacute sclerosing leukoencephalitis. The finding of inclusion bodies in cases of subacute sclerosing leukoencephalitis and the similarity of electroencephalographic tracings in subacute inclusion-body encephalitis leave little doubt as to the very close relationship, if not the complete identity, between the two conditions. As a third member of the group there must probably be added to these Pette and Döring's nodular panencephalitis. In 1950 Macken and Lhermitte[17] published an exhaustive analysis of the nosological situation of subacute sclerosing leukoencephalitis, and in 1953 Foley and Williams[11] added a review of the relationship between subacute sclerosing leukoencephalitis and subacute inclusion-body encephalitis.

The disease has frequently been misclassified as "Schilder's disease" or as "diffuse sclerosis," which falsely implies that it is a primary demyelinating disease. Case VI in Bouman's monograph on "Schilder's Disease" and Case X in Einarson and Neel's[10] extensive review of the diffuse scleroses are almost certainly instances of subacute sclerosing leukoencephalitis.

The histologic picture of subacute sclerosing leukoencephalitis has similarities to that seen in general paresis, and it resembles, both clinically and pathologically, the changes in cerebral trypanosomiasis.[12] This implies that such an inflammatory gliotic reaction is not necessarily specific for any one disease entity. The actual identity of the diseases belonging to the group of subacute encephalitides and the validity of such classification will have to await the discovery of an etiological agent. It is indeed interesting to speculate upon the fact that all the atypical encephalitides, among which might well be classified van Bogaert's, Pette and Döring's and Dawson's type, were reported after the disappearance of the great epidemics of acute encephalitis. As Lhermitte has suggested, it is possible that, because of the subacute course and because of the type of cerebral terrain upon which they are found, these three types of encephalitis may represent peculiar forms of an already known type of encephalitis.

SUMMARY AND CONCLUSIONS

Seven cases of subacute sclerosing leukoencephalitis of the van Bogaert type have been presented. Histopathologic findings in three of those cases, as well as representative electroencephalographic tracings, have been reported.

This disease entity is characterized clinically by a subacute progressive illness affecting children and consisting of intellectual and psychic deterioration, bilateral spasticity, and various types of dyskinesias and hyperkinesias, leading to decerebrate rigidity, dementia, and death. Pathologically the process consists of a diffuse, isomorphic gliosis with little demyelinization and strong inflammatory reaction mainly involving the subcortical white matter but also affecting the nuclear masses of the basal ganglia, the thalamus, and the brain stem. The electroencephalographic changes are characteristic and consist of rhythmic discharge complexes associated with but not the result of myoclonic jerks.

Subacute sclerosing leukoencephalitis is closely related to Dawson's subacute inclusion-body encephalitis and Pette-Döring's nodular panencephalitis. These three diseases form the

group of subacute encephalitides which is often confused with other diffuse encephalopathies of childhood.

We wish to express our thanks to the following physicians who were kind enough to furnish details concerning the clinical course of some of the cases included in this report: Drs. Cordier and Henneaux (La Hestre), Lefebvre (Antwerp), Kemps (Diest), Verspreeuwen (Antwerp), and W. P. Williamson (Kansas City, Kansas).

Dr. Ludo van Bogaert reviewed the histologic sections and gave constant help and advice.

REFERENCES

1. Akelaitis, A., and Zeldis, L.: Encephalitis With Intranuclear Inclusion Bodies, Arch. Neurol. & Psychiat. **47:** 353, 1942.
2. Balthasar, K.: Zur Kenntnis der Panencephalitis nodosa (Pette), Arch. Psychiat. **117:** 666, 1944.
3. Blackwood, W.: Brain Biopsy in Children With Progressive Dementia, Excerpta Med. (sect. VIII) **8:** 779, 1955.
4. Bouman, L.: Diffuse Sclerosis, Bristol, 1934, John Wright & Sons, Ltd.
5. Brain, R., Greenfield, J., and Russell, D.: Subacute Inclusion Encephalitis (Dawson Type), Brain **71:** 365, 1948.
6. Campbell, A., Guy, J., and Walter, W.: Two Cases of Cytomegalic Inclusion Encephalitis, Arch. Dis. Childhood **27:** 507, 1952.
7. Cobb, W., and Hill, D.: Electroencephalogram in Subacute Progressive Encephalitis, Brain **73:** 392, 1950.
8. Dawson, J.: Cellular Inclusions in Cerebral Lesions of Epidemic Encephalitis, Arch. Neurol. & Psychiat. **31:** 685, 1934.
9. Dubois, R., van Bogaert, L., and Lhermitte, F.: Deux nouvelles observations de leucoencéphalite sclérosante subaiguë, Acta neurol. et psychiat. belg. **49:** 762, 1949.
10. Einarson, L., and Neel, A.: Contribution to the Study of Diffuse Brain Sclerosis With a Comprehensive Review of the Problem and Report of Two Cases, Acta Jutland **14:** 1, 1942.
11. Foley, J., and Williams, D.: Inclusion Encephalitis and Its Relation to Subacute Sclerosing Leucoencephalitis, Quart. J. Med. **22:** 157, 1953.
12. Gallais, P., and Badier, M.: Recherches sur l'encéphalite de la trypanosomiase humaine africaine, Méd. trop. **6:** 633, 1952.
13. Geinert, F., and Müller, N.: Ueber die subakute sklerosierende Leuko-encephalitis, Arch. Psychiat. **193:** 51, 1955.
14. Landau, W., and Gitt, J.: Subacute Encephalitis: Three-Year Survival With Long-Term Remission, Neurology **2:** 488, 1952.
15. Lesse, S., Hoefer, P., and Austin, J.: Diffuse Encephalopathy Associated With Periodic Synchronous Abnormal Discharges in the Electroencephalogram, American Neurological Association 81st Meeting, 1956.
16. Lumsden, C.: Fundamental Problems in the Pathology of Multiple Sclerosis and Allied Demyelinating Diseases, Brit. M. J. **1:** 1035, 1951.
17. Macken, J., and Lhermitte, F.: Etude clinique et anatomique de la leucoencéphalite sclérosante subaiguë, Bull. Acad. roy. méd. belgique **15:** 205, 263, 1950.
18. Malamud, N., Haymaker, W., and Pinkerton, H.: Inclusion Encephalitis With a Clinico-Pathologic Report of Three Cases, Am. J. Path. **26:** 133, 1950.
19. Martin, F., Macken, J., and Hess, R.: Sur une encéphalite subaiguë ayant les charactères de la leucoencéphalite sclérosante, avec inclusions, Arch. Suisses Neurol. Psychiat. **66:** 217, 1950.
20. Pette, H., and Döring, G.: Ueber ein heimlische Panencephalomyelitis von Charakter des Encephalitis Japonica, Deutsche Ztschr. Nervenh. **149:** 7, 1939.
21. Poser, C., and van Bogaert, L.: The Natural History and Evolution of the Concept of Schilder's Diffuse Sclerosis, Acta psychiat. et neurol. **31:** 285, 1956.
22. Radermecker, J.: Aspects électroencéphalographiques dans trois cas d'encéphalite subaiguë, J. belge neurol. et psychiat. **49:** 222, 1949.
23. Radermecker, J.: Les aspects électroencéphalographiques dans les encéphalites de l'enfance, Bull. Soc. Clin. Hop. Civ. Charleroi **11:** 1, 1951.
24. Schilder, P.: Zur Kenntnis der sogenannten diffusen Sklerose, Ztschr. Neurol. Psychiat. **10:** 1, 1912.
25. Schilder, P.: Zur Frage der Encephalitis periaxialis diffusa, Ztschr. Neurol. Psychiat. **15:** 359, 1913.
26. Schilder, P.: Die Encephalitis periaxialis diffusa, Arch. Psychiat. **71:** 327, 1924.
27. van Bogaert, L.: Une leuco-encéphalite sclérosante subaiguë, J. Neurol., Neurosurg. & Psychiat. **8:** 101, 1945.
28. van Bogaert, L., and De Busscher, J.: Sur la sclérose inflammatoire de la substance blanche des hémisphères (Spielmeyer), Rev. neurol. **71:** 679, 1939.
29. Van Buren, J.: A Case of Subacute Inclusion Encephalitis Studied by the Metallic Methods, J. Neuropath. & Exper. Neurol. **13:** 230, 1954.

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LABORATORY AND CLINICAL STUDIES ON CANDIDIASIS IN THE NEWBORN INFANT

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THIS report deals with the clinical significance of *Candida albicans* in the oral cavity and the intestine of the newborn infant. *C. albicans* is considered a constituent of the normal human oral and intestinal flora.[1, 2] The frequency of its occurrence has been reported as 6 to 37 per cent in the mouth and as 15 to 31 per cent in the stools of healthy adults and children.[3, 4]

Information concerning the incidence of *C. albicans* in the newborn infant is of practical clinical importance. If the organism can occur as a saprophyte in the mouths of healthy newborn infants, then treatment is indicated only in the presence of acute clinical manifestations of candidiasis. If, on the other hand, the presence of *C. albicans* in the mouth of the newborn infant is correlated with a high incidence of clinical thrush, preventive treatment may be warranted before clinical symptoms become evident, obviating the necessity for isolation and special care of "thrush babies."

Reports on the incidence and significance of *C. albicans* in the mouth of newborn infants are somewhat conflicting. Epstein[5] found that only 50 per cent of the infants who harbored the organism developed thrush. On the basis of these findings, only cases with clinical manifestations should be treated. On the other hand, Anderson and others[6, 7] reported clinical thrush in 100 per cent of the infants from whose mouths the organism had previously been recovered. If this is correct, then preventive treatment would be justified upon isolation of *C. albicans.*

The only exhaustive study concerning the incidence of *C. albicans* in the intestine of healthy newborn infants is that of Epstein,[5] 1924, who found that 25 per cent of infants 2 to 6 weeks of age harbored "thrush fungus" in the intestine. Subsequent reports on the subject deal mainly with the presence or absence of *C. albicans* in the feces in conjunction with oral or cutaneous candidiasis.[8-11]

The present study attempts to reevaluate the occurrence and significance of *C. albicans* in the mouth and intestine of the newborn infant. By confirming a priori laboratory tests by subsequent clinical developments, we hope to provide a basis for an early diagnosis and possibly prophylactic treatment of oral thrush and other forms of candidiasis in the newborn nursery.

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This work was aided by a grant from the Squibb Institute for Medical Research, New Brunswick, N. J., and by the Jewish Philanthropic League of Brooklyn, N. Y.

Read at the Twenty-third Annual Meeting of the Mycological Society of America, Storrs, Conn., Aug. 27, 1956.

MATERIAL AND METHOD

Over a period of nine months at least two oral swabs and cultures have been taken routinely from 2,175 newborn infants, in such a way that a representative number of samples was obtained for each of the first seven days of life. Five hundred twenty stool samples were taken concurrently on the third, fourth, or fifth day of life.

Fig. 1.—Chlamydospore formation by *C. albicans* on polysaccharide medium. These distinctive spores are not formed in vivo.

The swabs were incubated overnight on Sabouraud agar slants, and smears were examined microscopically the next morning. This procedure was adopted after it was found that in the earliest stages of infection the organism is present in such small numbers as to escape detection when the smears were read immediately.

The cultures were kept for at least one week. *C. albicans* was identified on the basis of chlamydospore formation (Fig. 1) on "cream of rice"-Tween 80 agar,[12] and by its microscopic morphology in lesions. Yeast-like organisms which did not form chlamydospores were identified on the basis of their fermentation and utilization of dextrose, maltose, sucrose, and lactose.

RESULTS

A. Predictability and Pathogenesis of Oral Thrush.—C. albicans was recovered from the mouth of 82 out of 2,175 infants, or 3.77 per cent. This is about one-tenth of the frequency reported for healthy older children.[4] Sixty-seven of these 82 infants had positive oral smears from the third day of life onward. These infants were examined and swabbed once or twice daily until clinical signs appeared, or until they were discharged from the hospital at 8 or 9 days of age. Sixty-six infants developed oral thrush within one to five days after the first positive smear was obtained.

One infant with positive oral smears did not develop oral thrush but had cutaneous candidiasis in the diaper area. Thus, clinical oral thrush developed in 98.5 per cent of the infants in whom yeast forms had been demonstrated by microscopic examination.

Fifteen infants had negative smears but positive oral cultures. Of these, seven were lost from observation before the presence or absence of clinical manifestations could be established. Of the remaining eight infants, six had cutaneous candidiasis and two

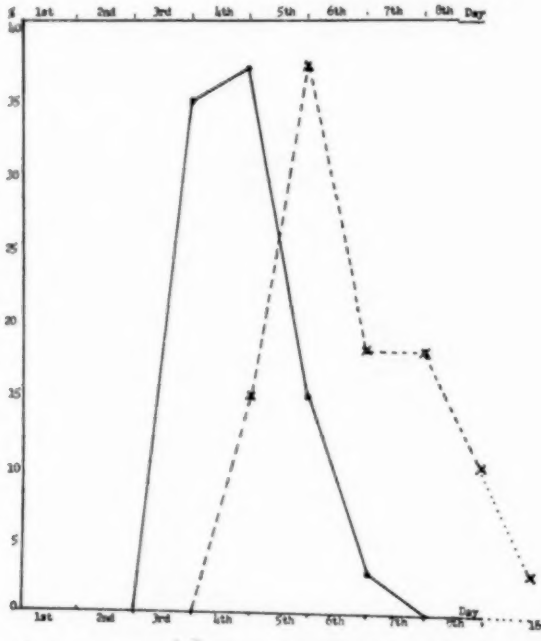

Fig. 2.—Graph showing the times of first detection of *C. albicans* in oral smears (solid line) and the onset of clinical thrush (broken line). In most cases *C. albicans* could be detected on the third or fourth day, while clinical manifestations appeared on the fifth or sixth day of life.

TABLE I. RELATION BETWEEN POSITIVE ORAL SMEARS AND/OR CULTURES AND CLINICAL CANDIDIASIS

MYCOLOGIC FINDINGS	TOTAL CASES	ORAL THRUSH ONLY	ORAL THRUSH AND SKIN LESIONS	SKIN LESIONS ONLY	TOTAL CLINICAL CANDIDIASIS	NO CLINICAL FINDINGS
Oral smear and culture positive for *C. albicans*	67*	28	38	1	67	0
Oral smear negative, culture positive for *C. albicans*	8	0	0	6	6	2
Oral smear and/or culture positive	75	28	38	7	73	2

Summary: 98.5 per cent of infants with positive oral smears developed oral thrush. 100 per cent of infants with positive oral smears developed clinical candidiasis.

*Stools were positive in all cases.

remained clinically negative. The findings obtained in seventy-five known cases are summarized in Table I.

The correlation between positive oral smears and the onset of clinical thrush is shown in Fig. 2. It will be noted that in the majority of cases the first positive laboratory findings were obtained on the third and fourth days of life, while the first clinical manifestations appeared on the fifth or sixth day, one to two days after *C. albicans* was first demonstrated in microscopic examination.

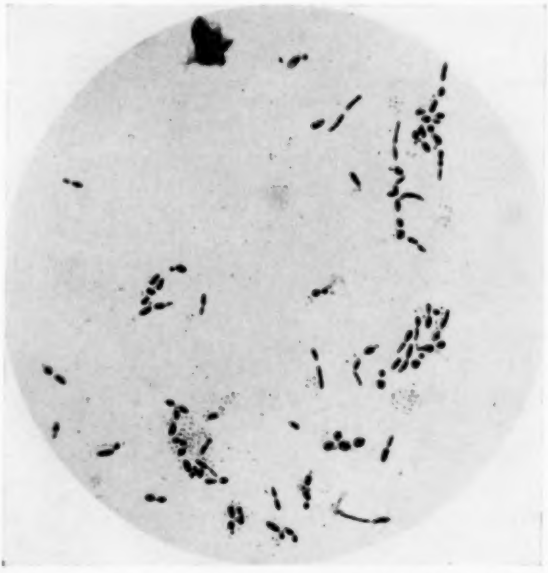

Fig. 3.—Photomicrograph of oral smear from an apparently healthy newborn infant after overnight incubation on Sabouraud's agar. Only budding spores (blastospores) are present.

Successive oral smears illustrated the progress in the development of thrush. In the preclinical stage variable numbers of blastospores were found exclusively, singly or in short chains. The organism occurred extracellularly only. Hyphae were absent (Fig. 3). The next stage was represented by invasion of the oral epithelium and the formation of small intracellular colonies of *C. albicans*. Filaments began to develop at this stage (Fig. 4), and from then on oral smears showed the spores and hyphae representing the typical pathognomonic picture of candidiasis (Fig. 5). Clinical thrush coincided with the first formation of hyphae, or became manifest within the next twelve to twenty-four hours.

The two cases with positive oral smears which failed to develop clinical thrush never showed hyphae, but only budding spores.

It appears, then, that clinical candidiasis is associated with tissue invasion and the development of hyphae. Little is known regarding the conditions favoring mycelium formation by *C. albicans* in vivo and the role of the

hyphae in the pathogenesis of candidiasis. Speculations concerning this phenomenon are outside the scope of the present report. The observations presented here indicate that *C. albicans* occurs in the saprophytic, nonpathogenic stage in the form of blastospores and extracellularly only, while in the parasitic, pathogenic stage both spores and hyphae are seen intracellularly as well as extracellularly. In this connection it is of interest to note that in monilial granuloma hyphae are found greatly in excess

Fig. 4.—Photomicrograph of oral smear from the same infant taken twenty-four hours later. Note colony of *C. albicans* within epithelial cell and formation of hyphae. Pin-point-sized thrush lesions may be present at this stage.

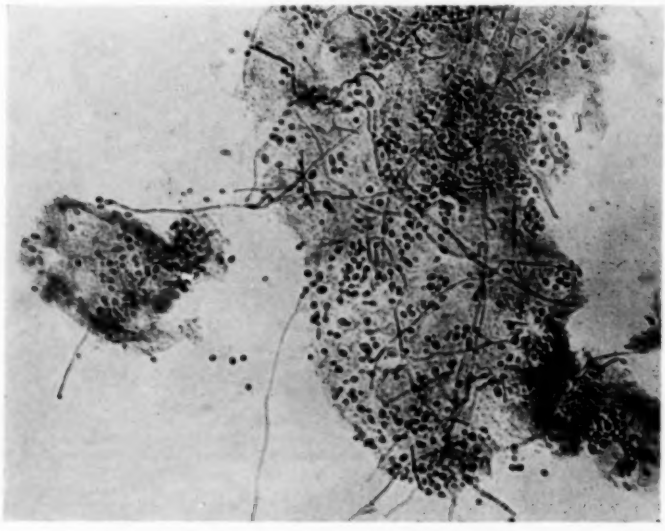

Fig. 5.—Photomicrograph of oral smear from full-blown thrush. Note colonization of oral epithelium and abundant mycelium formation.

of spores, almost simulating the histopathologic picture of dermatophytosis (Fig. 6).[13-15]

So far as oral thrush is concerned, the pathogenicity of *C. albicans* seems to be of a quantitative rather than qualitative nature. Our observations in that respect confirm the findings of other investigators.[3, 5] If the organism is present in sufficient numbers, so as to be easily detectable in direct smears, and if conditions for its proliferation and tissue invasion are favorable, then clinical manifestations will develop within a few days. If very few organisms are noted, even after overnight incubation of the specimen, clinical thrush will develop eight to ten days later (as it did in one case in the present series) or not at all. In such cases the organism may disappear from the oral cavity or at least become undetectable by laboratory methods. This is illustrated by the eight cases mentioned above which had negative oral smears and positive cultures. These showed scanty growth, and subsequent mouth cultures were negative. None of these eight infants developed oral thrush, although six of them developed cutaneous candidiasis in the diaper area (see Table I).

The observations presented here support those of Epstein[5] regarding the numerical importance of *C. albicans* in the pathogenesis of thrush, but cannot confirm the high incidence of nonclinical carriers (50 per cent) which he reported.

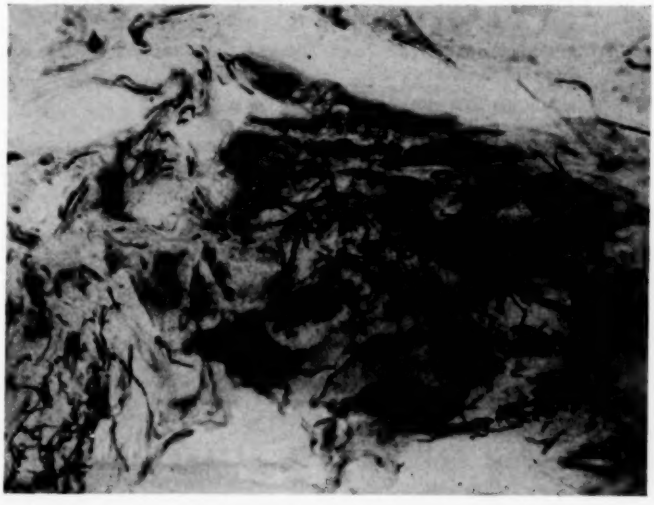

Fig. 6.—Histopathologic picture of monilial granuloma. Note predominance of mycelial forms of *C. albicans*.[14]

In agreement with Anderson and others,[6, 7] we find that oral thrush is predictable. However, it appears that a positive mouth culture need not invariably foreshadow clinical thrush. Our observations indicate that it is the direct smear which is of primary prognostic and diagnostic importance, since it furnishes information regarding the

quantity and morphology of the organisms present. However, it appears that *C. albicans* is rarely isolated from the mouths of healthy infants.

The present investigations indicate: (1) that oral thrush is predictable with almost 100 per cent certainty if the organism can be demonstrated in *direct smears* from the third or fourth day of life onward, and (2) that clinical thrush is present or imminent as soon as hyphae, indicating tissue invasion, are found.

lesions but no oral thrush.* Only one infant remained free of symptoms. In other words 97.8 per cent of infants harboring *C. albicans* in the intestine had clinical candidiasis in one form or another, with skin lesions present in almost 75 per cent.

These findings indicate that *C. albicans* does not ordinarily occur in the intestine of healthy newborn infants. This stands in marked contrast to conditions in adults and older children. In newborn infants *C. albicans* occurs

TABLE II. RELATION BETWEEN POSITIVE STOOL AND CLINICAL CANDIDIASIS

TOTAL POSITIVE SPECIMENS	ORAL THRUSH ONLY	ORAL THRUSH AND SKIN LESIONS	SKIN LESIONS ONLY	TOTAL CANDIDIASIS	NO CANDIDIASIS
47	11	23	12	46	1

Summary: 74.5 per cent of infants with positive stools had cutaneous candidiasis.
97.8 per cent of infants with positive stools had clinical candidiasis.

B. The Significance of C. albicans in the Intestine of the Newborn Infant.—In agreement with previous reports,[5, 8, 9] *C. albicans* was invariably found in the stools of patients with thrush. More than 50 per cent of these patients had cutaneous candidiasis in the perianal and diaper area. In view of these observations, it seemed important to investigate a larger group of infants. Out of 520 stool specimens taken routinely at the same time as oral samples, fifty-two yielded *C. albicans*. Three yielded nonpathogenic Candida species which were not associated with clinical manifestations. Five of the fifty-two babies harboring *C. albicans* were lost from observation. The distribution of clinical candidiasis in the remaining forty-seven cases is shown in Table II. It will be noted that thirty-four infants in this series had oral thrush, with or without skin lesions while twelve infants had skin relatively infrequently, and its presence is almost invariably indicative of clinical candidiasis in the mouth, the diaper area, or both.

SUMMARY AND CONCLUSIONS

1. *Candida albicans* cannot be regarded as a normal constituent of the microbial flora of the newborn infant. The presence of blastospores in oral smears from the third or fourth day of life onward permits prediction of clinical oral thrush within one to five days with almost 100 per cent certainty.

2. Oral thrush is present or imminent as soon as hyphae are found in direct oral smears.

3. The presence of *C. albicans* in the intestine of the newborn infant is

*The coincidence of oral thrush and cutaneous lesions might conceivably have been higher if the patients had not been treated immediately by oral administration of Mycostatin which tends to eliminate *C. albicans* from the intestine, thereby preventing cutaneous infection due to contact with the feces.[16]

closely associated with clinical candidiasis and predisposes to cutaneous lesions in the perianal and diaper area.

In view of these findings, we advocate routine swabbing of the newborn's mouth on the fourth day of life in order to detect potential cases of oral thrush. Treatment should be instituted when spores are found, and is definitely indicated if hyphae are present. Preferably such treatment should consist in oral rather than in topical medication in order to eliminate the organism from the digestive tract and to prevent cutaneous candidiasis resulting from contact with the infected feces.

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REFERENCES

1. Robinson, H. M.: Moniliasis Complicating Antibiotic Therapy, A. M. A. Arch. Dermat. & Syph. **70**: 640, 1954.
2. Reiss, F.: Candidiasis in Dermatology, Excerpta Medica, Dermatology and Venereology, vol. 10, No. 3, sect. 13, March, 1956.
3. Debré, R., Mozziconacci, P., Drouhet, E., Drouhet, V., and Hoppeler, A.: Les infections à Candida chez le nourrisson, Ann. paediat. **184**: 129, 1955.
4. Marples, M. J., and Di Menna, M. E.: The Incidence of Candida albicans in Dunedin, New Zealand J. Path. & Bact. **64**: 497, 1952.
5. Epstein, B.: Studien zur Soorkrankheit, Jahrb. Kinderheilk. **104**: 129, 1924.
6. Ludlam, G. B., and Henderson, J. L.: Neonatal Thrush in a Maternity Hospital, Lancet **1**: 64, 1942.
7. Anderson, N. A., Sage, D. N., and Spaulding, E. H.: Oral Moniliasis in Newborn Infants, Am. J. Dis. Child. **67**: 450, 1944.
8. Ibrahim, J.: Ueber eine Soormykose der Haut im frühen Säuglingsalter, Arch. Kinderheilk. **55**: 91, 1911.
9. Moro, E.: Eczema infantum und Dermatitis seborrhoides, Berlin, 1932, Julius Springer.
10. Mayer, J. B., Goetz, H., and Seitz, G.: Eine Epidemie von Soormykose der Haut unter dem Bilde der Erythrodermia desquamativa (Leiner), Ann. paediat. **177**: 213, 1951.
11. Holzel, A.: Skin Thrush in Early Infancy, Arch. Dis. Childhood **28**: 412, 1953.
12. Taschdjian, C. L.: Routine Identification of Candida albicans: Current Methods and a New Medium, Mycologia, in press.
13. Hauser, F. V., and Rothman, S.: Monilial Granuloma: Report of a Case and Review of the Literature, Arch. Dermat. & Syph. **61**: 297, 1950.
14. Pluss, J. M., and Kadas, L.: A Case of Monilial Granulomas Associated With Widespread Superficial Moniliasis and Epidermatophytosis, J. Invest. Dermat. **23**: 317, 1954.
15. Ruppert, M.: Ueber das Moniliagranulom, Ztschr. Haut- u. Geschlechtskr. **20**: 97, 1956.
16. Childs, A. J.: Effect of Nystatin on Growth of Candida albicans During Antibiotic Therapy, Brit. J. Med. **1**: 60, 1956.

THE UTILITY OF BLOOD OXYGENATION AS AN INDICATOR OF POSTNATAL CONDITION

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THE possibility of establishing a precise physiological index for identifying the clinical condition of anoxia is intriguing. Determination of oxygen saturation of the blood, as pioneered by Eastman[1] and developed further by Smith,[2] Taylor,[3] MacKinney,[4] Apgar,[5] and Pennoyer, Behrer, and Keso[6] offers just such a possibility. The contradictory results reported in the literature on the immediate and delayed effects of fetal and neonatal anoxia may in part be attributed to lack of precision in defining the condition. That is, what one investigator has termed anoxia might differ in several significant respects from what other investigators have studied. In animal studies, where the extent and duration of oxygen deprivation can be controlled more readily, a similar source of variability can be found in the variety of methods used for inducing anoxia (surgical intervention, placement in simulated high-altitude chambers, etc.).

Oxygen saturation of the blood as an objective measure of anoxia should have a distinct advantage over clinical estimates of degree of oxygen deprivation. Certainly greater community of meaning is encouraged when such a technique is used. Measurement in terms of a physiological condition capable of accurate assay makes theoretically possible the establishment of a cutting point below which anoxia exists and above which it does not exist.

In spite of the face validity of such a measure, it is still important to know something about the relationship of blood oxygen to other indicators of newborn status. In a previous paper,[7] using a sample of 323 infants delivered vaginally, we examined the effects on oxygen saturation of certain prenatal and perinatal factors. Oxygen saturation of cord blood was significantly affected by complications of delivery and by various anesthesias. Babies delivered under pudendal block or without anesthesia had significantly higher oxygen levels in the sample of cord blood and in a sample taken ten minutes after birth than did babies delivered under inhalation anesthetics or continuous caudal. No attempt was made to investigate specifically the

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relationship between blood oxygen and clinical status of the infant. However, some indirect evidence was found in the fact that only 21 per cent of the uncomplicated group of infants failed to achieve 90 per cent oxygenation by one hour, whereas 29 per cent of the prenatally complicated group and 37 per cent of the delivery-complicated group remained below this level. Of twenty-five infants requiring oxygen resuscitation, regardless of whether they occurred in the uncomplicated or complicated delivery groups, almost half still remained below the 90 per cent level at one hour.

However, no attempt was made to obtain a more comprehensive picture of the clinical condition than that indicated by use of resuscitative measures and quick appraisal of the infant's condition in the delivery room. In this paper we shall relate oxygen saturation to two criteria of newborn status: (1) to immediate postnatal clinical status, and (2) to performance on behavior tests given twenty-four to forty-eight hours after birth. Also we shall examine the patterning of sequential oxygen determinations during the first hour of postnatal life.

PROCEDURE

Subjects.—Subjects for the study were 323 infants, born in two St. Louis hospitals between 1953 and 1955, on whom oxygen saturations at birth and shortly after were determined. Of this number, 128 infants born in one of the hospitals were also given part or all of the Behavior Tests for the Newborn, developed by Graham.[8] Selection of the sample of infants was affected by time factors only; i.e., all infants for both the oxygen saturation and the Behavior Test subsamples were born during the daytime. There is no evidence to suggest that this time limitation introduces a selective bias. When two or more babies were born almost simultaneously and one of these seemed likely to have difficulties, the one for whom complications were expected was chosen. In a modern obstetrical hospital, extreme complications are the exception rather than the rule, and a special effort was made to get data on such cases whenever they appeared.

As our study was concerned with anoxia, it was especially desirable to include as many infants with respiratory difficulties as possible. However, because of the requirements of the experimental procedure, some of the infants most likely to have such difficulties were precisely the ones who could not be studied. For example, if the baby required vigorous resuscitation, it was difficult to get early blood samples. Thus the total sample did not include many infants who experienced severe anoxia as judged by clinical standards.

Oxygen Saturation.—Four samples of blood were drawn from each infant whenever this was feasible. Occasionally it was impossible to get all four samples on a given infant. The first sample was taken from the cord at the time of delivery, with subsequent samples taken at 10, 30, and 60 minutes after delivery. The later arterialized capillary samples were drawn from the heated heel of the infant. All samples were kept iced until the series for the infant was complete, at which time analysis was performed. Method of analysis was a

microadaptation of the spectrophotometric determination of oxyhemoglobin described by Roos and Rich.[9] Data are recorded in terms of per cent oxygen saturation. For a more detailed account of the procedure for collecting and analyzing the blood samples, the reader is referred to Pennoyer and associates.[8]

Anoxia Score.—This score represents an attempt to quantify events which are regarded as reflecting the clinical condition of anoxia during the neonatal period. In a previous paper[10] we have described a three-category Prognostic Score derived from weighting information found in the medical chart. The three categories are prenatal anoxia, postnatal anoxia, and postnatal signs of central nervous system injury. For the present analysis we were concerned only with the postnatal anoxia category, as there would be more reason to expect blood oxygen levels determined during the first hour of postnatal life to reflect the infant's clinical condition during that hour than to reflect prenatal anoxia or to forecast subsequent events likely to produce a central nervous system injury.

The Anoxia Score is derived from ratings made on the basis of information found in the hospital chart. There are inevitable differences of opinion regarding the importance of various clinical signs of anoxia. However, an attempt was made to assign weights in accordance with generally prevailing pediatric opinion. A measure of the clinical validity of ratings derived from this weighting system was determined by comparing scores so assigned with clinical judgments made by pediatricians experienced with neonates. Satisfactory inter-judge agreement was established, as was correspondence with clinical ratings. The Anoxia Score could range from zero to three, with higher scores indicating more severe anoxia. All 323 infants on whom blood oxygen determinations were made were assigned an Anoxia Score. This was done with no knowledge of the infant's level of blood oxygen.

Behavior Tests.—As these tests have been described in detail elsewhere,[8] only a brief description need be given here. The tests were developed in order to have available a reliable and valid method of assessing the behavioral status of the newborn infant. They have been shown to discriminate adequately between a group of traumatized and nontraumatized infants[11] and to show a close relationship to seriousness of clinical condition.[10] There are five tests in the battery: (1) a determination of Pain Threshold by the use of an electronic stimulator; (2) a Maturation Scale, adapted from Gesell, containing nine items; (3) a Vision Scale; (4) a rating of Muscle Tension; and (5) a rating of Irritability.

All babies were examined by the psychologist when they were between 24 and 48 hours old. For two reasons data from all tests are not available for every infant. First, the standardization of the various tests was completed at different times. It seemed unwise to sacrifice data from the first ones standardized in order to have only complete records. Second, it is not always possible to administer every test to every infant. For example, some infants reactive enough to be examined do not keep their eyes

open long enough to have their visual response observed. Scores for each separate test were converted to standard scores having a mean of 50 and a standard deviation of 10. This procedure permits relative performance on the different procedures to be immediately determined and also permits controlling for race differences and for age of infant at the time of testing. In the analyses reported in this paper, scores are always reported in standard score form.

RESULTS

Oxygen Saturation and Immediate Clinical Condition.—In Table I can be seen the mean oxygen saturation levels of groups differing in the degree to which they experienced what is generally designated clinically as postnatal anoxia. It is immediately apparent that the majority of infants in our sample showed no signs of postnatal anoxia and were accordingly given a zero Anoxia Score. Numbers of infants experiencing progressively more severe degrees of anoxia decrease sharply, with only four infants receiving relatively high scores (2.25 to 3.00). Oxygen saturations as determined from the cord sample tend to decrease as severity of anoxia increases, with one reversal of direction in the moderate range of anoxia scores. However, as will be noted in Table I, the number of infants experiencing moderate or severe clinical anoxia was small, and the means for those cases are consequently less stable. In the 60-minute sample no trend is detectable, with the four anoxic infants as well oxygenated (94.3 per cent) as the larger group who showed no signs of clinical anoxia (94.4 per cent).

TABLE I. MEAN OXYGEN SATURATION OF GROUPS HAVING DIFFERENT DEGREES OF POSTNATAL ANOXIA

	ANOXIA SCORE				
	(LOW) 0	0.25-1.00	1.25-2.00	(HIGH) 2.25-3.00	TOTAL N
Cord sample					
Number of cases	243	49	7	4	303
Mean O_2 per cent	62.3	50.8	57.6	34.0	
60-minute sample					
Number of cases	225	44	10	4	283
Mean O_2 per cent	94.4	91.2	89.2	94.3	

TABLE II. CORRELATION BETWEEN ANOXIA SCORE AND OXYGEN SATURATION

VARIABLES	N	r	SIGNIFICANCE LEVEL
Cord sample and Anoxia Score	272	–0.27	0.01
60-minute sample and Anoxia Score	272	–0.12	---

A more precise estimate of the relationship between oxygen saturation and postnatal anoxia can be seen in Table II, where correlations between these variables are reported. Subjects for this analysis were the 272 infants out of the total sample for whom both cord and one hour samples were available. The correlation of –0.27 based on the cord sample is statistically significant; i.e., there is a tendency for infants with high

anoxia scores to have low oxygen levels in samples of cord blood. However, this relationship is so small as to be of little or no practical significance. Within one hour after birth even this slight relationship has disappeared, as indicated by the nonsignificant correlation of –0.12.

These findings suggest that there is some relationship between blood oxygenation and those clinical signs ordinarily thought to signify postnatal anoxia, but that whatever relationship exists is time-bound. That is, a sample of blood taken from the cord is slightly, but not usefully, related to a concurrent condition, and one taken from the heel after sixty minutes of postnatal life will tell us nothing about whether or not a baby, at any time during that interval, *had* such a condition. If we are interested in finding a physiological index of clinical anoxia, we must conclude that the oxygenation of the blood does not provide such an index.

Oxygen Saturation and Performance on Behavior Tests.—Relationship between oxygen levels and behavior has been estimated in two ways. First, correlations between oxygen level and score on the Behavior Tests were calculated, and, second, differences between extreme groups have been examined.

In Table III may be seen the correlations between oxygen saturation and scores on each of the five behavior tests and the average standard score which combines data from three or more tests. For these correlations, the cord and 10-minute oxygen determinations and the 30-minute and 60-minute determinations were averaged. As the last two determinations are more stable and indicate something about the physiological status of the infant after independent respiration is securely established, it might be expected that data from these readings would be better predictors of the status of the infants at 24 hours. At the same time, the reduction in range of oxygen measures in these later readings would tend to reduce the size of any obtained correlations.

As is apparent in Table III, only one of the correlations obtained significance at the .05 level. This was the correlation between the Maturation Scale and the average of the 30-minute and 60-minute oxygen reading. Despite the fact that this correlation is statistically significant, it is low and would be of little practical benefit in prediction. Furthermore,

TABLE III. CORRELATIONS BETWEEN OXYGEN SATURATION AND BEHAVIOR TESTS

	N	CORD AND 10′	30′ AND 60′
		r	r
Pain	128	+0.07	+0.16
Maturation Scale	82	–0.16	+0.28*
Irritability	97	–0.07	–0.13
Tension	97	0.00	–0.04
Vision	73	+0.06	+0.03
Average Standard Score	99	–0.07	+0.06

*Significant at the .05 level.

when as many as twelve correlations are made, it is quite likely that one would be significant at the .05 level by chance. Combining tests does not increase the correlation with oxygen levels. That is, correlation for the average standard score on three or more of the tests with both oxygen measures fails to attain significance. From these data one would have to conclude that oxygen level of the

blood at birth is unrelated at 24 hours to the type of behavior measured in this study.

A second way of estimating a relationship between two variables is to take from the total sample extreme groups selected on the basis of one of the variables and then test for significant differences between these groups on the other variable. Often a pattern exists with respect to extreme conditions on two variables which does not hold within the middle range. For example, babies who are very poorly oxygenated at birth might show considerable impairment of performance on the behavior tests and those who are exceptionally well oxygenated might show a superior performance, even in the absence of a discernible pattern for the large number of infants whose oxygen saturations cluster about the average level.

For this analysis, extreme groups were selected in two ways. First, the cord sample only was considered. From the sample of 128 infants on whom both oxygen levels and behavior test scores were available, data were analyzed for all infants whose cord oxygen was *below* 30 per cent saturation and all those whose cord oxygen was *above* 80 per cent saturation. In Table IV are seen the results of this analysis. Only one difference attained statistical significance, and this difference is in the reverse direction from what would be expected. That is, the group having low cord oxygen levels had a higher performance on the Maturation Scale than did the group with high cord readings.

It is interesting to note that this difference occurs on the Maturation Scale, the only one of the five tests to show a low but significant correlation (0.28) with oxygen levels at one hour. Yet on this same test an inverse but nonsignificant correlation had been found between test score and cord reading. This reversal of direction is difficult to explain on logical grounds and, in the absence of other evidence, should probably be attributed to the random fluctuation which will occasionally obtain significance levels.

TABLE IV. BEHAVIOR TEST SCORES FOR LOW (<30 PER CENT) AND HIGH (>80 PER CENT) CORD OXYGEN GROUPS

	N	MEAN	DIFF.	t
Pain				
Low O_2	19	49.11	.85	.25
High O_2	26	49.96		
Maturation Scale				
Low O_2	15	54.27	6.67	2.60*
High O_2	20	47.60		
Vision				
Low O_2	14	44.14	2.00	.38
High O_2	14	46.14		
Irritability				
Low O_2	17	46.06	1.24	.44
High O_2	20	47.30		
Tension				
Low O_2	17	46.35	1.85	.73
High O_2	20	44.50		
Average				
Low O_2	17	48.24	1.39	.79
High O_2	20	46.85		

*Significant at the .05 level.

Since we were seeking to determine the effects of oxygenation on performance measured twenty-four to forty-eight hours later, it seemed possible that the cord sample was not the best one to use for establishing our extreme groups. Accordingly we made a selection which would take into account not only this early level of oxygenation but also the rate of rise to normal levels. All those infants having oxygen saturations below 75 per cent at 10 minutes and still below 85 per cent at either 30 or

60 minutes comprised the new low oxygen group. All those having saturations above 85 per cent at 10 minutes and above 90 per cent at 30 and 60 minutes made up the high oxygen group. In Table V are reported the results of this analysis. None of the differences is statistically significant. On the Pain Threshold the difference

TABLE V. BEHAVIOR TEST SCORES FOR LOW AND HIGH OXYGEN GROUPS

	N	MEAN	DIFF.	t
Pain Threshoid				
Low O_2*	20	43.05	7.80	1.85
High O_2†	34	50.85		
Maturation Scale				
Low O_2	15	47.33	3.98	1.25
High O_2	16	51.31		
Vision Scale				
Low O_2	12	52.50	2.93	.90
High O_2	14	49.57		
Irritability Rating				
Low O_2	16	47.31	2.53	.78
High O_2	18	44.78		
Tension Rating				
Low O_2	16	44.00	1.39	.39
High O_2	18	42.61		
Average Standard Score				
Low O_2	16	47.38	1.00	.48
High O_2	24	46.38		

*Low O_2 group consists of those cases with oxygen saturations below 75 per cent at 10 minutes and below 85 per cent at 30 or 60 minutes.

†High O_2 group consists of those cases with oxygen saturations above 85 per cent at 10 minutes and above 90 per cent at both 30 and 60 minutes.

in favor of the high oxygen group approaches statistical significance ($0.10 > P > .05$). However, on the remaining tests whatever differences appeared may be interpreted as random fluctuation around the total group mean. Thus, even when only extreme cases are used, there is no consistent pattern suggesting a superiority of the highly oxygenated group of infants when performance on the Behavior Tests for the Newborn is used as a criterion.

Sequential Oxygen Saturations.—Data from our study are in essential agreement with results reported from other laboratories[3, 4] that oxygenation of the infant's blood at the moment of birth is around 60 per cent saturation and that within a very short time after birth it rises to normal adult levels. A composite curve showing rate of rise for all the uncomplicated vaginal deliveries (N = 244) in our series is produced as Fig. 1. This composite, while adequately summarizing the group data, reveals nothing about the rate of rise in individual cases; nor does it elucidate in any way the importance of the early readings for predicting later oxygen levels.

We have examined our data in a way that would shed light on the relationship between early and later oxygen levels. Again, both correlation and dichotomous groupings were used for the analysis.

TABLE VI. CORRELATIONS BETWEEN EARLY AND LATE OXYGEN SATURATION LEVELS

VARIABLES	N	r	SIGNIFICANCE LEVEL
Cord and 60-minute sample	251	.09	---
10- and 60-minute sample	260	.29	.01

In Table VI can be seen the correlations between early and late oxygen saturations in all cases with both blood samples, except those infants receiving oxygen resuscitation. We were primarily concerned with the

predictive utility of the cord sample, for it was the cord reading which most clearly reflected the effects of various anesthesias and complications of delivery. As is apparent in Table VI, there is no relationship between the cord and the 60-minute readings ($r = .09$) which indicates that one cannot predict whether a baby will be well oxygenated at one hour on the basis of oxygen saturation of cord blood. This finding of no relationship is consistent with that of Smith and Kaplan,[2, p. 858] who found "little correlation between the state of oxygenation in the umbilical cord blood at the moment of birth and the time required for postnatal adjustment of blood oxygen content in the individual infant."

The reading taken at 10 minutes shows some relationship with later oxygenation, as reflected by a correlation of .29 with the 60-minute sample, but the correlation is still too small to be of any practical use.

In another attempt to determine the influence of cord oxygen on later oxygenation, we dichotomized the entire sample (except for those infants who received oxygen resuscitation) into infants having cord readings above and below 50 per cent saturation. The frequency of infants in each group having saturations below 90 per cent at one hour was then observed, and the resulting distribution tested for a relationship by means of chi square. Results of this analysis

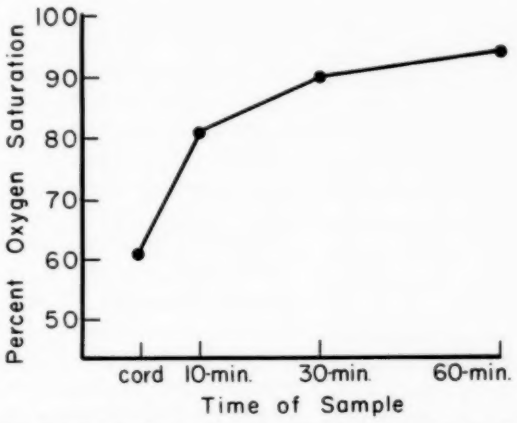

Fig. 1.—Changes in blood oxygen saturation during the first hour of life in 244 uncomplicated vaginal deliveries.

TABLE VII. PROPORTION OF INFANTS WITH CORD READINGS ABOVE AND BELOW 50 PER CENT HAVING O_2 LEVELS BELOW 90 PER CENT AT ONE HOUR

CORD READINGS	UNCOMPLICATED CASES		COMPLICATED CASES		TOTAL CASES	
	N	BELOW 90% AT 60 MIN.	N	BELOW 90% AT 60 MIN.	N	BELOW 90% AT 60 MIN.
50	50	.22	12	.75	62	.32
50	151	.20	38	.37	189	.23
Total	201		50		251	
	$X^2 = .02$		$X^2 = 3.92^*$		$X^2 = 2.04$	

*Significant at the .05 level of probability.

are seen in Table VII, with complicated and uncomplicated cases considered separately as well as together. Complicated cases were all those with either complications of pregnancy or with a delivery other than controlled spontaneous or low forceps. For the uncomplicated cases, there is no greater likelihood that an infant with cord oxygen below 50 per cent will have a 60-minute reading below 90 per cent than there is if the cord reading is greater than 50 per cent. The same is true when complicated and uncomplicated cases are combined, although the distribution is made less random by the addition of the complicated cases ($X^2 = 2.04$, $.20 > P > .10$). Consideration of the complicated cases separately shows a clear relationship. That is, cases with either fetal or delivery complications whose cord readings are below 50 per cent have a greater likelihood ($X^2 = 3.92$, $P = .05$) of being less than 90 per cent oxygenated at one hour than do complicated cases with cord readings above 50 per cent. A larger number (37 per cent) of the complicated cases with 50 per cent cord readings also remained below 90 per cent at one hour than was true of the uncomplicated cases.

DISCUSSION

An analysis of the data presented here raises the pertinent question of what sort of information is given by a determination of oxygen saturation. That is, we know that the amount of oxygen in the blood is measured, but we know little about what this means in terms of effect upon the total organism. Most investigators have tended to attribute to the measure an automatic validity, that is, to assume that a low blood oxygen saturation is synonymous with anoxia in the body tissues, particularly those of the central nervous system. By thus being designated as an infallible criterion, the measure has been exempt from rigorous investigation of its correlates.

In some of the recent studies employing quantitative determinations of oxygen saturation, the oxygen measure has been used as the dependent variable and the effects of certain independent variables upon it studied. For example, in the study by Taylor and associates,[3] the effects of various maternal anesthetic agents upon oxygen saturation was investigated and a differential effect reported. Likewise, MacKinney and coworkers[4] have reported on the effects of different types of deliveries on oxygenation during the first hour. Apgar and associates,[5] on the other hand, use oxygen saturation as the independent variable and investigate the relationship between level of oxygenation and later development. In this study, no significant correlation was found between levels of blood oxygen during the first three hours of life and intelligence during early childhood.

In the present series of studies[6–8, 10, 11] we have attempted to combine these approaches. In an earlier report the influence of anesthesias and of perinatal complications on oxygen saturation was presented. In the present paper we are concerned with the utility of the oxygen measure for summarizing a concurrent clinical condition or for predicting something about the status of the infant twenty-four to forty-eight hours later. If it

cannot do these things, it should not necessarily be expected to predict status at a point distant in time, after which many new variables may have confounded the situation.

In general, the results were disappointing. The cord oxygen showed a low but significant correlation with clinical estimates of postnatal anoxia, but the 60-minute sample did not show such a relationship in the total series. Likewise, the relationship between oxygen and behavior was essentially random. This lack of relationship between oxygen and behavioral status does not seem startling when the lack of relationship between early and late oxygen levels is taken into consideration. That is, if the cord reading is not useful for predicting later readings within the same physiological dimension and with very little lapse in time, it should not be surprising that it does not predict across dimensions (i.e., from blood physiology to behavior) after considerable lapse of time.

These findings suggest that oxygen saturation provides a precise and sensitive measure of what is occurring *at the moment*, but that it is relatively inadequate to reflect what occurred just prior to that moment or to predict what will happen during the next moment. It is possibly too limited in time perspective to be valuable in predicting the later status of an individual child.

The measure may be very sensitive and quite valuable in detecting effects of conditions occurring close in time, such as in reflecting effects of anesthesia and complications of delivery. In this connection it is interesting that in a previous study[7] we reported that the presence of prenatal complications and complications during labor did not affect the oxygen saturation as long as the delivery itself was uncomplicated. However, the frequency of infants requiring oxygen resuscitation and judged to be in poor clinical condition was significantly greater in this group than in a group without these complications. Oxygen saturation may be too drastically affected by what is happening at the moment to be able to reflect accurately those events with longer-lasting effects and with probably greater significance for the infant's development.

A final point should be made regarding the definition of anoxia—a point with which we were concerned at the beginning of this paper. It was suggested that some of the differences reported by various investigators on the effects of anoxia stem from differences in definition of the clinical condition. It was also suggested that the use of oxygen saturations presented a way of assuring uniform definition of anoxia and thus possibly making for greater ease of generalization from one study to another. A review of our results would suggest that to equate a certain level of oxygen saturation with what is clinically regarded as anoxia would be hazardous. Perhaps one of the most obvious difficulties is the fact that the postnatal oxygen determinations tell us little about the oxygen economy of the fetus prior to the time of birth, although, as Smith and Kaplan[2] have reminded us, there is a tendency to assume that they do. If fetal anoxia is likely to leave residual damage, as there is considerable evidence to suggest, then use of oxygen determination as a measure of

clinical anoxia excludes this vital category from consideration and possibly forces a definition too narrow to have broad clinical relevance.

Until it can be shown that oxygen saturation of the blood provides a precise measure of pathological anoxia of central nervous system tissues, it would not seem safe to assert, on the basis of lack of correlation between oxygen measures and later performance on gross psychological tests, that *anoxia* has no effect on later development. All that can legitimately be stated is that low oxygen levels in the cord or in the first hour of postnatal life apparently have no such effects.

SUMMARY

In the present study we have attempted to relate level of blood oxygen to the state of the infant at or near the time of birth. Oxygen levels were correlated to clinical ratings of anoxia and to performance on the Behavior Tests for the Newborn. A low but significant relationship between cord oxygen and clinically observed anoxia was found. There was, however, no relationship between immediate postnatal anoxia and oxygen level at one hour.

There was essentially no relationship between oxygen and performance on behavioral tests made when the infants were from 24 to 48 hours of age, although we have found previously that there is a relationship between these tests and the seriousness of the clinical condition. Also, there was no difference in performance on Behavior Tests between extreme groups selected on the basis of oxygen levels. Groups selected because of low cord oxygen or low oxygen throughout the first hour of life did not perform in a manner that was significantly different from groups whose oxygen readings were exceptionally high. The one exception to this was in the reverse direction from what would have been predicted; i.e., the low oxygen group performed better than the high oxygen group.

The patterning of early and late oxygen readings was examined. No correlation was found between the cord sample and the 60-minute sample, and the correlation between the 10- and 60-minute samples was low, although statistically significant. In the total group of both uncomplicated and complicated deliveries, infants having cord oxygen above the 50 per cent level showed no greater tendency to be above 90 per cent at one hour than did infants with cord readings below 50 per cent. In complicated deliveries only, those infants with cord readings below 50 per cent were significantly less well oxygenated at one hour than were those whose cord readings were above 50 per cent.

It was concluded that the measure of oxygen saturation, while having high face validity and objectivity, does not provide an entirely satisfactory measure of what is clinically regarded as anoxia. The cord sample, which should be the most revealing of the oxygen economy of the infant at the moment of birth, appears likely to be influenced by events of the moment and is unreliable as a predictor of later oxygen status. It was suggested that one of the difficulties with the oxygen measure is the fact that it is too sensitive to transitory states to be serviceable in predicting long-term effects upon the organism.

REFERENCES

1. Eastman, N. J.: Foetal Blood Studies, I. Oxygen Relationships of Umbilical Cord Blood at Birth, Bull. Johns Hopkins Hosp. **47**: 221, 1930.
2. Smith, C. A., and Kaplan, E.: Adjustment of Blood Oxygen Levels in Neonatal Life, Am. J. Dis. Child. **64**: 843, 1942.
3. Taylor, E. S., Goven, C. D., and Scott, W. C.: Oxygen Saturation of the Blood of the Newborn as Affected by Maternal Anesthetic Agents, Am. J. Obst. & Gynec. **61**: 840, 1951.
4. MacKinney, L. G., Ehrlich, F. E., and Chase, H. C.: A Study of Factors Affecting the Neurologic Status of Young Children. I. Place of Study and Some Neonatal Findings, Am. J. Pub. Health **45**: 653, 1955.
5. Apgar, V., Girdany, B. R., McIntosh, R., and Taylor, H. C., Jr.: Neonatal Anoxia. I. A Study of the Relation of Oxygenation at Birth to Intellectual Development, Pediatrics **15**: 653, 1955.
6. Pennoyer, M. M., Behrer, M. R., and Keso, M. G.: The Microspectrophotometric Determination of Blood Oxygen Saturation in Infants and Children, J. PEDIAT. **50**: 44, 1957.
7. Pennoyer, M. M., Graham, F. K., Hartmann, A. F., Sr., and others: The Relationship of Paranatal Experience to Oxygen Saturation in Newborn Infants, J. PEDIAT. **49**: 685, 1956.
8. Graham, F. K.: Behavioral Differences Between Normal and Traumatized Newborns. I. The Test Procedures, Psychol. Monogr. **70**: no. 427, 1956.
9. Roos, A., and Rich, J. A.: Spectrophotometric Determination of Oxyhemoglobin Saturation and Oxygen Content of the Blood, J. Lab. & Clin. Med. **40**: 431, 1952.
10. Graham, F. K., Pennoyer, M. M., Caldwell, B. M., Greenman, M., and Hartmann, A. F.: Relationship Between Clinical Status and Behavior Test Performance in a Newborn Group With Histories Suggesting Anoxia, J. PEDIAT. **50**: 177, 1957.
11. Graham, F. K., Matarazzo, R., and Caldwell, B. M.: Behavioral Differences Between Normal and Traumatized Newborns. II. Standardization, Reliability and Validity, Psychol. Monogr. **70**: no. 428, 1956.

Measles in the Year 1670

The measles most usually disappear about the eighth day, at which time, the vulgar (deceived by their reckoning in cases of smallpox) insist that they have *struck in*. In reality, however, they have finished their course. Thus it is believed that those symptoms which come on as the measles go off, are occasioned by their being struck in too soon; for it must be noted, that just at the time in question, the fever and the difficulty in breathing increase, and the cough becomes so harassing, that the patient can sleep neither night nor day. Infants, especially when they have been subjected to the hot regimen, and patients generally who have had recourse to hot remedies for the sake of promoting the eruption, are liable to these symptoms—symptoms which show themselves just as the measles give way. Hence, they may be thrown into a peripneumony, and this kills more patients than either the smallpox itself, or any symptom connected therewith. Yet, provided that the measles are properly treated, they are free from danger.

THOMAS SYDENHAM

HEREDITARY SPHEROCYTOSIS IN INFANCY

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WITH THE TECHNICAL ASSISTANCE OF J. M. MCKENTY, R.T.

CERTAIN characteristic manifestations of hereditary spherocytosis during infancy have been described by Abt[1] and Debré and associates.[2] The different symptomatology, the demonstration of normal red cell morphology and osmotic fragility, and the frequent absence of known family history of the disease may result in diagnostic difficulty. In addition this group of infants frequently receive transfusions prior to complete investigation and the donor blood may mask the true hematological and serological picture. These features were all encountered in the case reported below. Recently Dacie[3] has described additional diagnostic procedures for the investigation of hemolytic anemias. The results of two of these, namely, osmotic fragility after incubation and the rate of autohemolysis, were of value in establishing the early diagnosis and the probable hereditary derivation of the disease in this patient.

CASE REPORT

G. T. was born on Feb. 27, 1955, of a healthy primipara after an uncomplicated pregnancy. The labor was prolonged. Birth weight was 6 pounds. The infant was described as pale at birth. The mother was Rh negative and had never received a transfusion. Cord blood studies revealed a negative Coombs test. The cord hemoglobin value was 19 grams per 100 ml. and markedly increased numbers of immature red cells were noted in the film of the peripheral blood. The baby was not jaundiced during the first week or subsequently. The liver and spleen were enlarged and firm. Further hemoglobin values reported during the first week of life were 17 and 15 grams 100 per ml.

At the end of the first month of life he was very pale and the hemoglobin value was found to be 6 grams per 100 ml. Spherocytosis was not observed. One hundred forty milliliters of whole blood was given at 4 weeks and 200 ml. of whole blood at 9 weeks of age. The baby was admitted to the Health Centre for Children on June 2, 1955, for investigation of continuing unexplained anemia.

There was no family history of anemia, jaundice, or splenectomy. However, both maternal and paternal grandmothers had had cholycystectomies in their later years.

On examination at this time he was a well-developed and well-nourished infant and weighed 11 pounds 12 ounces. There was marked pallor but no icterus of the skin or sclera. The liver was enlarged to 3 cm. and the spleen to 4 cm. below the costal margin. The remainder of the examination was noncontributory.

During the ensuing four and one-half months he was studied in and out of hospital, employing a variety of hematological and serological techniques. A tentative diagnosis of hereditary spherocytosis was made and splenectomy was performed on Oct. 15,

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1955. He was readmitted to hospital on Dec. 2, 1955, with pneumococcal meningitis, and he responded well to antibiotic therapy. When last seen in June, 1956, the hemoglobin value was 12.9 grams per 100 ml. and red count was 4.96 million per cubic millimeter. Reticulocyte counts and bilirubin estimations were within normal limits.

TABLE I. SUMMARY OF LABORATORY FINDINGS OF PATIENT

DATE OF TEST	AGE WHEN TESTED	HEMOGLOBIN (GRAMS/100 ML.)	RBC (M/CU.MM.)	RETICULOCYTES (PER CENT)	SERUM BILIRUBIN (MG./100 ML.)
1955					
Feb. 27	1 da.	19.0			
28		17.0			
Mar. 4		15.5			
27	4 wk.	6.0			
Mar. 28		70 ml. whole blood			
29		70 ml. whole blood			
May 4	2 mo.	100 ml. whole blood			
5		100 ml. whole blood			
May 5		9.5			
10		11.1			
June 2	3 mo.	8.5	3.3	5.3	
5					0.8
7		7.7	3.2	5.2	1.3
15		7.6		8.3	
22		7.2		7.6	
July 6	4 mo.	7.3	3.19	8.8	1.8
July 7		150 ml. sedimented cells			
July 9		11.3	4.34	3.5	
19		9.7	3.86	1.1	
25		8.6	3.38	4.5	
Aug. 4	5 mo.	7.87	3.06	6.4	
11		7.38	3.04	7.3	2.5
18		6.93	2.92	7.5	2.0
30		7.3	2.92	0.8	
Sept. 13	6 mo.	6.3	2.78	4.0	
Oct. 3	7 mo.	5.9	2.7	7.1	
13		8.1	3.1		
Oct. 15		Splenectomy			
18		11.0	4.2		
20		12.0	4.6		
24		12.4	5.1		
1956					
Mar. 2	12 mo.	13.84		1.3	0.9
June 28	16 mo.	12.9	4.96		

Laboratory Findings.—The routine laboratory findings are set out in Table I. There was a constant microcytic anemia. Reticulocytosis was also present. Spherocytes were few at first but became more numerous by the fourth month of life. Initially the serum bilirubin was normal, but subsequent preoperative values were elevated. Postoperatively the serum bilirubin was normal.

Studies on mother and father and a paternal uncle are set out in Table II. The father showed a high normal hemoglobin value and red cell count

and an elevated reticulocyte count. Slight anisocytosis characterized his red cell morphology and spherocytosis was not seen. The serum bilirubin was slightly elevated on one occasion, but was normal on other tests. The paternal uncle also showed a high normal hemoglobin and an elevated serum bilirubin. Similar studies on the mother all gave normal results.

Osmotic Fragility: The results of osmotic fragility studies on the baby and father, using the method of Parpart and associates,[4] are shown in the form of fragility curves in Figs. 1 and 2. The results after incubation at 37° C. for twenty-four hours are noted in Fig. 3.

Autohemolysis: Using the method of Dacie,[3] quantitative estimations were made on the amount of spontaneous hemolysis occurring in twenty-four hours at 37° C. in the blood of the patient and his parents. The following results were obtained:

Normal	Lysis 0 to 0.5%	in 24 hours
Patient (June 23, 1955)	Lysis 0.9%	in 24 hours
Father (June 30, 1955)	Lysis 1.08%	in 24 hours
Mother (June 30, 1955)	Lysis 0.073%	in 24 hours

Red-Cell Survival Study: On July 7, 1955, the patient was given 150 ml.

TABLE II. SUMMARY OF LABORATORY FINDINGS IN PATIENT'S MOTHER, FATHER, AND PATERNAL UNCLE

DATE OF TEST	HEMOGLOBIN (GRAMS/100 ML.)	RBC (M/CU.MM.)	RETICULOCYTES (PER CENT)	SERUM BILIRUBIN (MG./100 ML.)
Patient's mother				
June 2, 1955	13.6	4.7	1.4	
29	13.3		0.7	
Patient's father				
June 7, 1955	16.9	5.75	2.3	
29	16.7		1.8	
Aug. 30	16.17		1.9	1.7
Sept. 13*	15.6	5.25	2.4	1.0
Oct. 4	16.05			0.6
Dec. 1	16.5		2.1	
March 2, 1956	16.1	5.23	2.1	0.1
Patient's uncle				
June 19, 1955	17.1	5.12	1.0	1.8

*Gave transfusion on September 11.

In Fig. 1 it is seen that initial fragility of the patient at 4 months of age was normal. It is of interest that there was increased fragility of the patient's cells after incubation (Fig. 3) at this time. Subsequent tests on the patient at 5 and 7 months and at 1 year showed marked increase in fragility. Studies on the father revealed normal osmotic fragility (Fig. 2) but increased fragility after incubation (Fig. 3). The osmotic fragility of the mother's cells was normal before and after incubation.

of sedimented red cells, Group O M cde/cde. Serial samples of the recipient's cells were suspended in a potent anti-N serum and the unagglutinated cells (donor) were counted and the results are recorded in Fig. 4. This shows normal survival of donor cells and supports the concept of an intrinsic red cell defect.

Serological Studies: The patient was O N Rh positive (probably CDe/cde). Serial serological investigations were

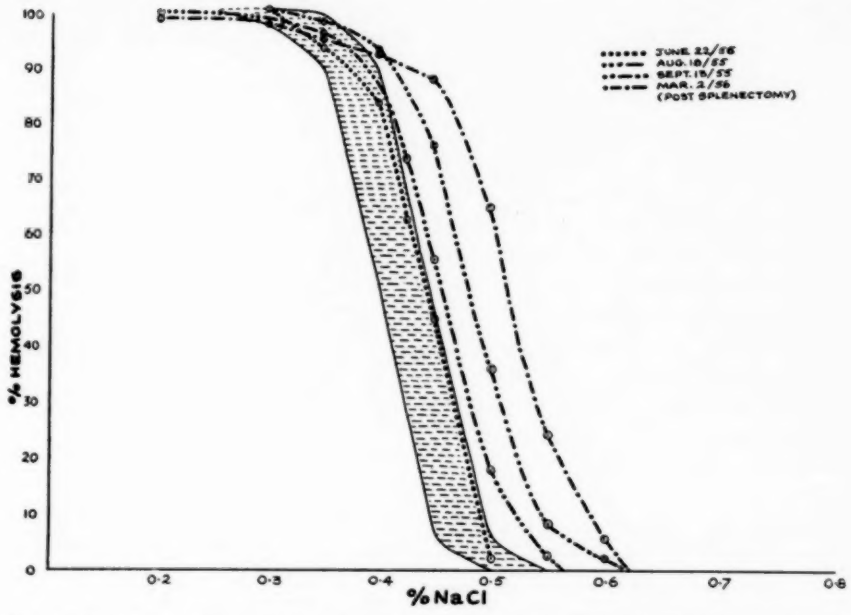

Fig. 1.—Osmotic fragility curves of patient (G. T.). The stippled area represents the normal range.

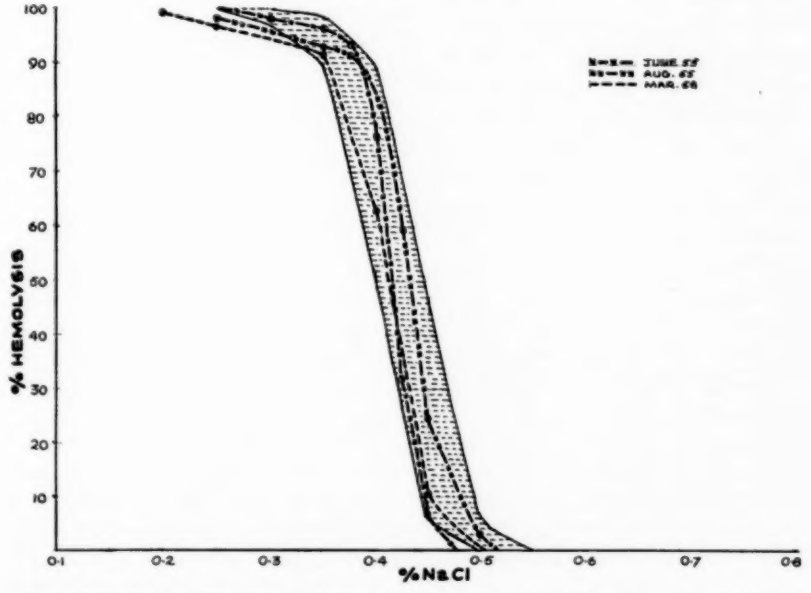

Fig. 2.—Osmotic fragility curves of father (L. T.). The stippled area represents the normal range.

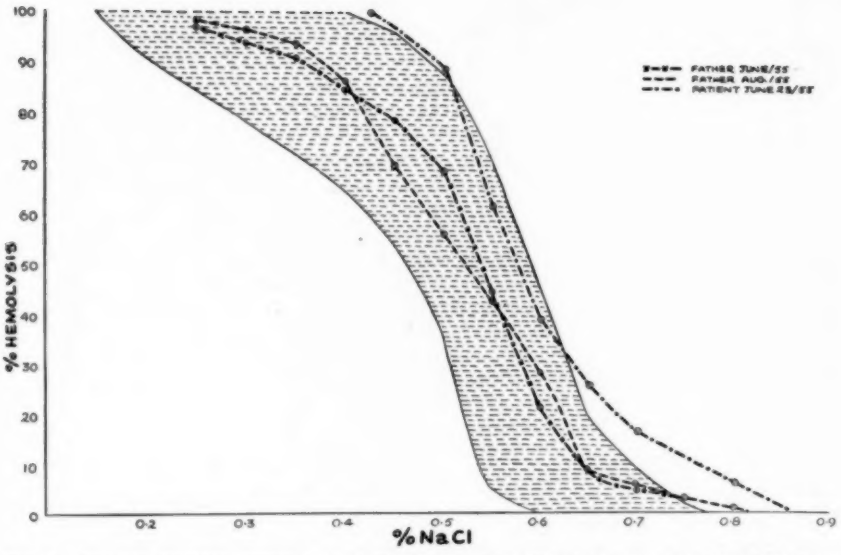

Fig. 3.—Osmotic fragility curves of patient (G. T.) and father (L. T.) after incubation at 37° C. for twenty-four hours. The stippled area represents the normal range.

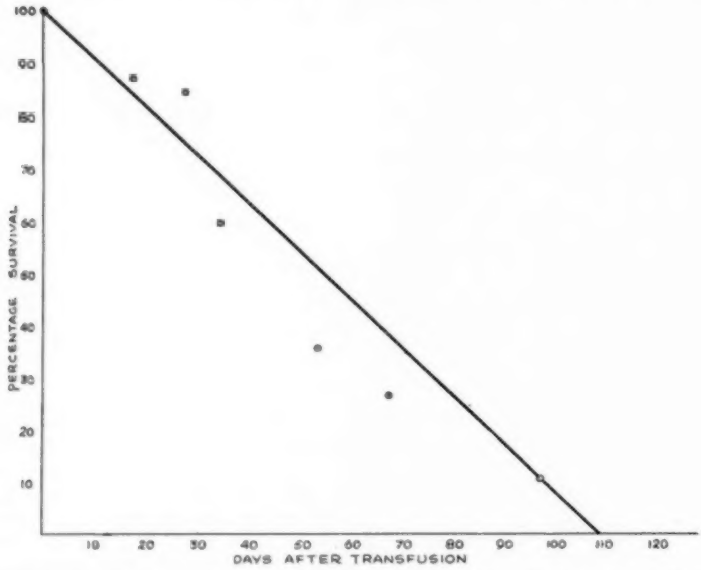

Fig. 4.—Survival of donor cells transfused to patient (G. T.). Patient, Group O CDe/cde N, and donor, Group O cde/cde M.

performed on the patient at monthly intervals from birth till October, 1955, and the findings were not helpful. The direct Coombs test was negative and no abnormal antibodies were demonstrated in the patient's serum. The mother was O Rh negative (cde/cde) and no Rh antibody was found, nor was any "family" antibody demonstrated. The father was A_1 Rh positive (probably CDe/cde). No serological abnormality was demonstrated.

COMMENT

This patient presented the problem of severe anemia in the first month of life. The cord hemoglobin value was within normal limits and the direct Coombs test was negative. Spherocytosis and anemia were not present during the first week of life. At 3 months, red cell morphology, serum bilirubin, and osmotic fragility studies were normal. It is probable that the multiple transfusions were responsible for these findings and that we were studying a mixed cell population in which donor cells predominated. The incubated fragility curve was abnormal at 3 months, which suggested the presence of a small proportion of fragile red cells.

Further studies revealed continuing pallor and splenomegaly with anemia, reticulocytosis, increased serum bilirubin, and the gradual appearance of spherocytosis and abnormal osmotic fragility curves. The serological findings excluded an acquired hemolytic mechanism based on blood group isoimmunization or auto-antibody formation, and suggested the diagnosis of a congenital hemolytic anemia. The gradual appearance of spherocytosis and the demonstration of abnormal fragility curves were compatible with the diagnosis of hereditary spherocytosis. The normal survival of transfused donor cells in the patient and the equivocal hematological findings in the father and paternal uncle supported this possibility.

Abt,[1] Debré and co-workers,[2] and Newns[5] have emphasized that hereditary spherocytosis may be recognized during infancy, and the majority of reported cases have been diagnosed after 3 or 4 months of age. Macaulay[6] reviewed the cases studied in the neonatal period. Newns[5] has pointed out the similar clinical and hematological features in hemolytic disease due to Rh iso-immunization and hereditary spherocytosis during crisis. Hemolytic disease due to major blood group incompatibility may well prove a more difficult differential diagnostic problem in the neonatal period, because spherocytosis and increased osmotic fragility are commonly present and the direct Coombs test is often negative in the latter condition. Roddy[7] described two infants in the same family who developed hemolytic episodes during the neonatal period. Their mother had hereditary spherocytosis and this diagnosis was made in the infants. The first developed hyperbilirubinemia and signs of kernicterus on the fourth day. In the second case an exchange transfusion was done at 86 hours when the serum bilirubin was 26.6 mg. per cent, and the infant escaped brain damage.

Abt[1] and Debré and associates[2] emphasized a difference in symptomatology when the disease is manifest during infancy. Anemia is a more prominent feature than jaundice, which may be entirely lacking. The onset of the anemia may be insidious or severe hemolytic crises may occur.

Splenic enlargement is characteristically more marked than in older children and adults. The above picture, associated with spherocytosis and increased osmotic fragility, may be associated with either hereditary spherocytosis or an acquired hemolytic mechanism. In such cases serological demonstration of antibodies must be sought.

Normal osmotic fragility has been noted in several reported cases.[1, 2, 8] Newns[5] mentions two cases in which the fragility was normal in infancy but increased at a later age. In our case it was normal at 4 months, although after incubation at 37° C. for twenty-four hours increased fragility was demonstrated.

Abt[1] and Newns[5] have made the surprising observation that a family history of the disease is frequently lacking in cases which are recognized in infancy. In our patient, the father's hematological findings were near the borderline of abnormality as evidenced by the high normal hemoglobin, red cell, and reticulocyte counts. On one occasion his serum bilirubin was elevated. Though his red cells showed normal osmotic fragility curves, following incubation at 37° C. for twenty-four hours, fragility was abnormal and his rate of autohemolysis was increased. These findings suggest that he may have a compensated form of the disease. The preliminary findings of the paternal uncle were similar to the patient's father, but we have been unable to do the additional studies in our laboratory. In view of the unexplained high incidence of normal family histories in the reported cases, it seems reasonable that more detailed investigations would reveal evidence of mild disease in more families.

The occurrence of meningitis during the second postoperative month is of considerable interest. In 1952, King and Shumacker[9] described a series of approximately 100 splenectomies, five of which were done before 6 months of age for hereditary spherocytosis. Four of the five developed meningitis from six weeks to three years postoperatively, and one of the four died. The fifth infant died three weeks postoperatively following a short febrile illness of unknown nature. They suggested a causal relationship between removal of the spleen and susceptibility to infection in this age group. Gofstein and Gellis[10] reviewed 107 splenectomies and they noted a correlation between splenectomy and subsequent infection in four cases. However, they did not confirm the age relationship noted above.

It follows that parents and physicians should be alerted to the possibility of serious infections after splenectomy, particularly in infants and young children.

SUMMARY

A case of hereditary spherocytosis posed a difficult diagnostic problem during the first months of life. Spherocytosis was not observed during the neonatal period. The classification of the hemolytic anemia was partially obscured by the presence of a large proportion of donor blood. A normal family history contributed to the delay in diagnosis.

The application of uncommonly used techniques, namely, osmotic fragility after incubation, the rate of autohemolysis, and red cell survival studies, elicited valuable information.

The patient developed pneumococcal meningitis six weeks after splenectomy.

REFERENCES

1. Abt., A. F.: Hemolytic Disease in Infants, Am. J. Dis. Child. **60**: 812, 1940.
2. Debré, R., Lamy, M., Sée, G., and Schramcek, G.: Congenital and Familial Hemolytic Disease in Children, Am. J. Dis. Child. **56**: 1189, 1938.
3. Dacie, J. V.: The Haemolytic Anaemias, London, 1954, J. & A. Churchill, Ltd., p. 478.
4. Parpart, A. K., Lorenz, P. B., Parpart, E. R., Gregg, J. R., and Chase, A. M.: The Osmotic Resistance (Fragility) of Human Red Cells, J. Clin. Invest. **26**: 636, 1947.
5. Newns, G.: Acholuric Jaundice in Infancy, Great Ormond St. J. (no. 1), p. 32, 1951.
6. Macaulay, D.: Acholuric Jaundice in a Newborn Infant, Arch. Dis. Childhood **26**: 241, 1951.
7. Roddy, R. (ed.): Clinical Conference at St. Christopher's Hospital for Children, Philadelphia. Two Cases of Hereditary Spherocytosis Manifest in the Newborn Period, J. PEDIAT. **44**: 213, 1954.
8. Schiff, E.: Congenital Hemolytic Anemia With Normal Fragility of the Red Blood Cells, Arch. Dis. Childhood **13**: 264, 1938.
9. King, H., and Shumacker, H. B.: Splenic Studies: I. Susceptibility to Infection After Splenectomy, Ann. Surg. **136**: 239, 1952.
10. Gofstein, R., and Gellis, S. S.: Splenectomy in Infants and Children. The Question of Overwhelming Infection Following Splenectomy, A. M. A. Am. J. Dis. Child. **91**: 566, 1956.

Treatment of Acidosis in 1832

I have just seen the operation of transfusion, in a case of malignant cholera, performed by Dr. F. T. Ferris. The subject was Mrs. Rice, No. 105 Broome street, about 50 years of age.

Before the operation was performed, this female appeared to be in the last stage of disease; she had lost the power of speech; she had no pulse; her extremities and tongue were cold; her hands and feet blue, and her whole appearance indicated immediate dissolution.—Dr. Ferris was in attendance, and as the last resort performed the operation of transfusing into the veins a quantity of warm water, impregnated with muriate and sub carbonate of soda. The breathing became natural, the pulse gradually appeared at the wrist, the heat of the surface was restored, the natural color of the skin re-appeared, her voice became natural, and in fact she was *literally restored from death to life.* Her eyes, from being glassy and death-like, became natural and sprightly; her voice was strong, and she actually began to direct some of the domestic concerns of her family. I left her about two hours after the operation had been commenced, expressing her gratitude to the doctor, for his exertions, and thanking her God for her comparative restoration.

I send you this hasty account of the operation for publication, hoping the doctor himself will soon give a more minute detail of the case.

H. M. D.

FROM THE AMERICAN MERCURY, July 30, 1832.

HEREDITARY CEREBRAL PALSY

A Preliminary Report

Johanna Blumel, Ph.D., E. Burke Evans, M.D., and G. W. N. Eggers, M.D.
Galveston, Texas

THE clinical syndromes described by Little[9] and now classified under the general term "cerebral palsy" include conditions known as spastic paralysis, athetosis, ataxia, rigidity and tremors, and various subdivisions and combinations of these manifestations. A comprehensive classification was established by the great pioneer in this field, Winthrop M. Phelps,[13] who selected "cerebral palsy" as the most accurate description of this condition. The American Academy for Cerebral Palsy[2] defines this term as "any abnormal alteration of movement or motor function arising from defect, injury, or disease of the nervous tissue contained in the cranial cavity."[2]

The types of cerebral palsy arising from injury or disease of the nervous tissue have been quite thoroughly studied by investigators, and much has been written on the subject, especially since about 1920, when interest in cerebral-palsied children began to increase. The literature on various aspects of cerebral palsy is voluminous, and it is not the purpose of this paper to review and evalute it. Our interest concerns the genetic aspect of this condition or the "defect . . . of the nervous tissue contained in the cranial cavity," assuming that occasionally the "defect" is due to the genotype of the individual.

Some genetic anomalies, such as cleft palate, clubfoot, congenital dislocation of the hips, and polydactylia, can be corrected by modern orthopedic and plastic surgery. However, very little effective anatomical correction by surgery is appropriate for the manifestations of cerebral palsy. According to Eggers[5] only a few surgical procedures are of real value to these individuals, and only approximately 20 per cent are acceptable for surgery. Courville,[3] in his study of the etiology of cerebral palsy in 1,254 cases, shows that the largest group are those of unknown origin. Other causes in decreasing order are birth factors, antenatal factors, postnatal illness, erythroblastosis, trauma, and tumor.

Perlstein,[12] in his classification of cerebral palsy according to etiology, states that "by hereditary conditions are meant those that are genetically transmitted, may involve racial or familial predilection, and are often sex-linked. These may be either static or progressive in nature." In discussing predisposing factors Perlstein[11] contends that cerebral palsy is more common among first-born children, occurs more frequently in children born to older women, and is more frequent in boys, who on the average weigh more

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This research was aided in part by a grant from the United States Public Health Service.

than girls at birth. Greenspan and Deaver,[7] in a study of ninety-four cases, concluded that sex, age of mother, and being first born were not predisposing factors to cerebral palsy.

This example of opposite findings, which might be due to a number of factors, including sampling errors in the particular group under investigation and insufficient numbers, is presented here only to show that the solution of this challenging problem requires a multidisciplined approach in which the geneticist must play a vital part.

Some of the literature[1, 4, 6, 7, 10, 14-16] dealing with the etiology of cerebral palsy was reviewed, and certain studies pointed to genetic factors in at least part of the large group of unknown etiology. A study was therefore undertaken to determine the types of inheritance responsible for some of these clinical manifestations.

Our approach to the problem was to investigate those families with more than one cerebral-palsied child. The facilities and records of the Moody State School for Cerebral Palsied Children were made available to us for this study. The children admitted to this school are selected, and only those between the ages of 5 and 12 are accepted. Admission requires recommendation by a medical doctor, a cerebral palsy center, or some other outpatient treatment institution. There are thirty-three outpatient cerebral palsy centers affiliated with the Texas Society of Crippled Children. The facilities of the school are available to any child in the state selected by a screening committee of six members, consisting of an orthopedic surgeon, pediatrician, psychologist, director of the school, director of nursing, and the head of the special education department. This committee carefully reviews all pertinent data and determines whether or not a child will benefit from the concentrated training program and has the opportunity for continuous follow-up treatment.

As of Aug. 31, 1956, 250 cerebral-palsied children have been accepted at the Moody State School for evaluation, treatment, and training since it began to operate in 1950. In the families of this group of cerebral-palsied children nine families had more than one affected child.

CASE HISTORIES

The pedigree presented diagrammatically in Fig. 1 represents four generations. The Roman figures on the left indicate generations, and the Arabic figures locate individuals. This pedigree was established by examination of medical records, correspondence with persons who attended the people, and a personal interview with the mother and older brother of the propositi, IV-14 and IV-16.

CASE 1 (IV-14, Fig. 1).—History on admission April 17, 1955: This Mexican male child, born Oct. 28, 1944, was the fourth-born child of this union. This was a full-term child with nothing in the history to indicate difficulty at birth. Apparently his condition after birth was also normal. There was no evidence of jaundice or cyanosis, and no difficulty with nursing. The child sat alone at the age of 12 months, crawled at 1½ years of age, and talked when he was 2 years old. However, he still does not stand or walk alone. A slight nystagmus is also present. He had been diagnosed as a spastic quadriplegia, but there was some question as to the validity of this diagnosis. An obturator neurectomy had been performed in 1951, leaving him "more handicapped than

helped." After a great deal of discussion the boy was diagnosed as "essentially spastic paraplegia," and "congenital anomaly" was given as the etiological agent. The child was discharged March 30, 1956, and at that time given a progress rating of "good." Ratings at the school are as follows: poor, fair, satisfactory, good, and excellent.

CASE 2 (IV-16, Fig. 1).—History on admission April 17, 1955: This Mexican male child, the younger brother of Case 1, was born on April 7, 1947. His history is very similar to that of Case 1. There was nothing unusual in birth or in the prenatal or postnatal periods. The boy has a definite lateral nystagmus and was diagnosed as a "spastic with cerebellar pathway involvement." It was the consensus of the group that "he is very much like his brother, only more so."

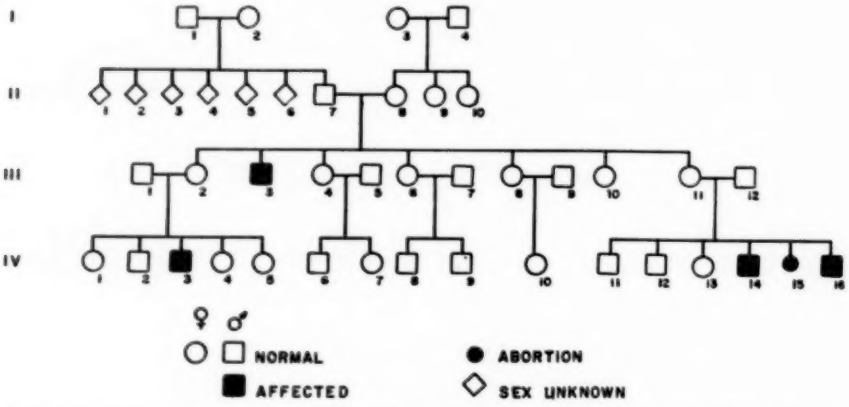

Fig. 1.—A pedigree of a family group demonstrating sex-linked inheritance for cerebral palsy. Roman figures on the left indicate generations. Arabic figures locate individuals.

PEDIGREE

Examination of Fig. 1 reveals that the propositi, IV-14, and IV-16 have three normal siblings, IV-11, IV-12, and IV-13, respectively. We also wish to point out that there was an abortion, for no apparent reason, between the births of the two affected sons. Going back to the next generation we find that the uncle, III-3, the only male child in this generation, also has cerebral palsy. So far, two of the females, III-2 and III-11, have produced offspring with cerebral palsy. III-10 is dead, but III-4, III 6, and III-8, potential transmitters of the trait up to the present writing, have only produced phenotypically normal children. The number of children born of these unions is small compared with the two unions that have transmitted the trait to half of their sons and possibly produced daughters who are carriers of the trait. The possibility that affected children may yet be produced by III-4, III-6, and III-8 remains.

Our pedigree indicates that II-8 transmitted the trait to her only son and at least two of her daughters, III-2 and III-11. II-8 may have received the trait from her mother who died in 1928 at age 78, or there may have been a mutation in her germ plasma. The conditions are comparable to the well-known sex-linked case

of hemophilia transmitted by Queen Victoria.[8] Unfortunately we were not able to get any information on II-9 and II-10 who could also be carriers if the trait had actually been transmitted from I-3 to II-8, which certainly is one possibility. These individuals reside in Mexico and our informant had not kept in touch.

All four of the affected males in our pedigree manifest a similar spastic type of involvement. IV-3 has the same type, including eye involvement, as IV-14, except that he is more handicapped because he has had no treatment. According to III-11, her brother III-3 is just like her sons IV-14 and IV-16.

As stated above, of interest also is the abortion between the births of our propositi. Since abortions are more frequent in families where so-called pathological genes operate to produce malformed progeny, it is apparently nature's way of taking care of these would-be abnormal children. If all such aborted embryos, from mothers with other cerebral-palsied children, were studied histologically, no doubt a great deal of light might be shed on the developmental aspect of the nervous system for these entities. The more severe involvement of IV-16 may be due to the fact that genes causing malformations seem to operate more often in older women, e.g., more mongols are born to older women. Whatever it is that causes the genes to exert their influence or lack of influence must be operating to a greater degree in the older individual and thus may exert its effect earlier in the development, producing greater involvement.

Perlstein's[12] reference to sex-linked inheritance as one of the causes of cerebral palsy and the frequent allusions in the literature[4, 7, 10, 14-16] to relatives, brothers, and cousins with cerebral palsy, usually without mention of sex, prompted us to report our pedigree of what is apparently a sex-linked type of inherited cerebral palsy. This preliminary paper is published with the hope that present investigators of the etiology of cerebral palsy will seriously consider the genetic aspect of these manifestations. Research of this nature is of necessity time-consuming. Personal interviews are mandatory and even then one finds a great deal of reticence regarding afflictions of relatives.

SUMMARY AND CONCLUSION

The pattern of inheritance illustrated in Fig. 1 clearly indicates sex-linkage. It will be observed that the trait is transmitted through the mother to approximately one-half of her sons. This type of inheritance for cerebral palsy may very well explain the slightly higher incidence of cerebral palsy in the male population. With the etiology unknown in the majority of cases of cerebral palsy it is conceivable that several types of inheritance give a similar clinical picture.

A family group is presented, demonstrating sex-linked inheritance for cerebral palsy.

Appreciation is extended to Miss Robertine St. James, Director of the Moody State School for Cerebral Palsied Children, for her help and cooperation in this study.

REFERENCES

1. Asher, P., and Schonell, F. E.: Arch. Dis. Childhood 25: 124, 1950.
2. Cardwell, Viola E.: Cerebral Palsy Association for the Aid of Crippled Children, 1956.
3. Courville, Cyril Brian: Cerebral Palsy, Los Angeles, 1954, San Lucas Press.

4. Davel, J. G.: South African M. J. **25**: 817, 1951.
5. Eggers, G. W. N.: Personal communication.
6. Evans, P. R.: Arch. Dis. Childhood **23**: 213, 1948.
7. Greenspan, Leon, and Deaver, George G.: Arch. Phys. Med. **34**: 478, 1953.
8. Iltis, Hugo: J. Hered. **39**: 113, 1948.
9. Little, William John: Lancet **2**: 378, 1861.
10. Penrose, L. S.: A Clinical and Genetic Study of 1,280 Cases of Mental Defect, London, 1938, Medical Research Council, Special Report Series, No. 229, His Majesty's Stationery Office.
11. Perlstein, Meyer A.: Nerv. Child. **8**: 128, 1949.
12. Perlstein, Meyer A.: J. A. M. A. **149**: 30, 1952.
13. Phelps, Winthrop M.: Crippled Child. **26**: 4, 1948.
14. Towbin, A.: A. M. A. Arch. Path. **59**: 397, 1955.
15. Yannet, Herman: J. PEDIAT. **24**: 38, 1944.
16. Yue, S. J.: Am. J. Phys. Med. **34**: 335, 1955.

Debility of the Lower Extremities

The disorder intended here is not noticed by any medical writer within the compass of my reading, or is not so described as to ascertain the disease. It is not a common disorder, I believe, and seems to occur seldomer in *London* than in some other parts. Nor am I enough acquainted with it to be fully satisfied, either in regard to the true cause, or seat of the disease, either from my own observation, or that of others; and I have myself never had opportunity of examining the body of any child who has died of this complaint. I shall therefore only describe its symptoms, and mention the several means attempting for its cure, in order to induce other practitioners to pay attention to it.

It seems to arise from debility, and usually attacks children previously reduced by fever; seldom those under one, or more than four or five years old. It is a chronical complaint, and not attended with any affection of the urinary bladder, nor with pain, fever, nor any manifest disease; so that the first thing observed is a debility of the lower extremities, which gradually become more infirm, and after a few weeks are unable to support the body. There are no signs of worms, or other foulness of the bowels; . . .

When only one of the lower extremities has been affected, the above means, in two instances out of five or six, entirely removed the complaint: but when both have been paralytic, nothing has seemed to do any good but irons to the legs, for the support of the limbs, and enabling the patient to walk. At the end of four or five years, some have by this means got better, in proportion as they have acquired general strength: but even some of these have been disposed to fall afterwards into pulmonary consumption, where the debility has not been entirely removed.

MICHAEL UNDERWOOD, 1789.

THE CHLORIDE CONCENTRATION OF SALIVA AND SWEAT IN INFANCY

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PATIENTS with cystic fibrosis of the pancreas have a high concentration of chlorides in the saliva.[1] These patients frequently harbor the staphylococcus in the nose and throat.[2] It has been suggested that there may be a relation between these two observations, the staphylococcus being more resistant to high salt concentrations than other microorganisms.[3] Since the staphylococcus is also a frequent inhabitant of the nose and throat of infants in premature and newborn nurseries,[4] it was decided to investigate the chloride concentration of their saliva. The results of these studies led to a broadening of the investigation to include infants and children up to 10 years of age, and also to an investigation of the chloride concentration in sweat in nursery infants.

METHOD

Saliva was collected as suggested by McGrady and Bessman.[1] Weighed cotton pledgets were placed inside the cheek next to Stensen's duct. In nursery infants where the volume of saliva was often small, one pledget was placed next to each duct and the infant permitted to suck on a nipple during the collection. Collections were made two to three hours after feeding, and the collection period lasted five to ten minutes. The volume of collected saliva was determined gravimetrically, the saliva was eluted from the cotton with 10 c.c. of distilled water, and the chloride concentration determined on a 5 c.c. aliquot by the method of Schales and Schales.[5]

Sweat was collected by placing the infants in plastic sacs as suggested by Schwachman.[6] Because of the low volumes of sweat, gauze pledgets were placed on both the abdomen and back. Chloride analyses were performed as for the saliva. In several instances, in order to secure adequate collections,

TABLE I. CONCENTRATION OF CHLORIDES IN SWEAT (MEQ./LITER) IN NURSERY INFANTS

	AGE (DAYS)	BIRTH WEIGHT (GRAMS)	CHLORIDES
1	2	3,800	9
2	4	2,950	13
3	6	2,500	12
4	7	1,950	9
5	7	1,500	17
6	8	1,975	5
7	11	1,640	13
8	12	1,700	9
9	12	1,630	20
10	13	1,673	7
11	18	1,530	7
12	19	2,200	10
13	20	1,790	14
14	21	1,350	11
15	39	1,480	20
16	42	1,500	8
17	45	1,550	12
18	56	1,530	9

From the Department of Pediatrics, New York University-Bellevue Medical Center.

Aided by a grant from the Cystic Fibrosis Association.

*John and Mary R. Markle Scholar in Medical Sciences.

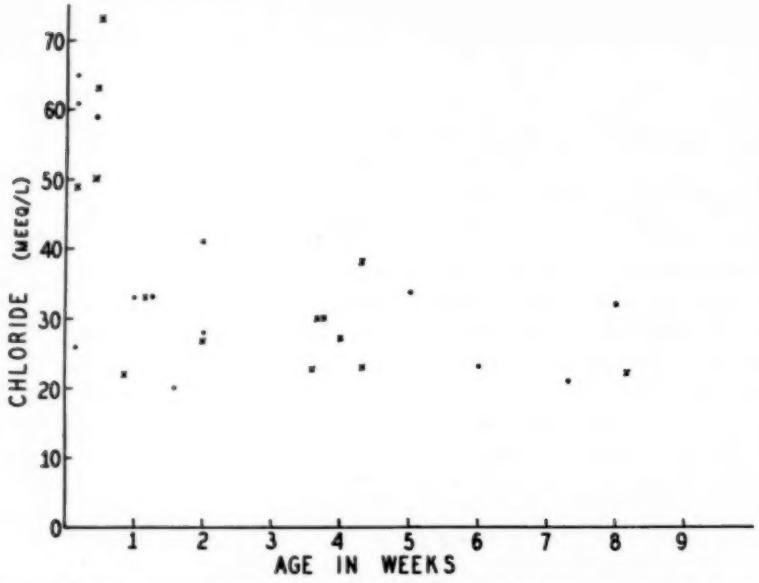

Fig. 1.—Chloride concentration in salvia in premature and term infants from birth to 8 weeks of age. x, Premature infants. •, Term infants.

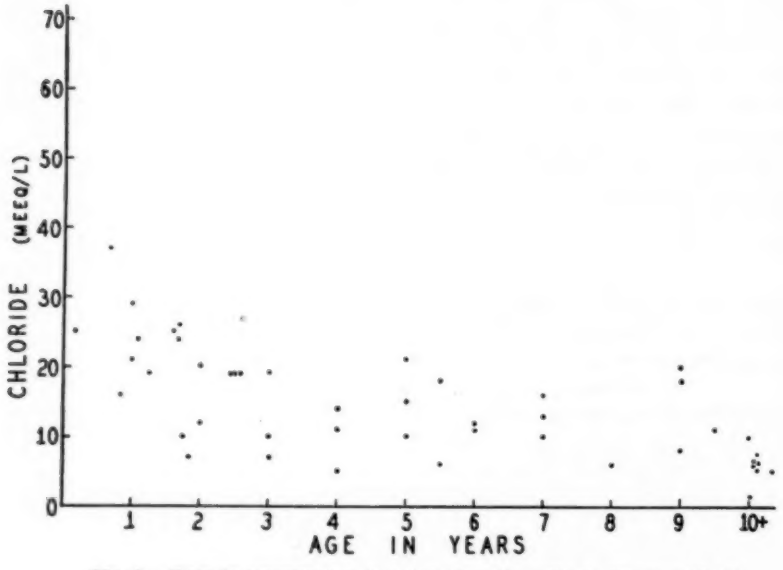

Fig. 2.—Chloride concentration in saliva from 2 months to 10 years of age.

the infants were placed in an incubator with the temperature maintained at 90° F. Collection periods were from one to two hours. Collections of less than 150 mg. were discarded.

RESULTS

In Fig. 1 are presented the chloride concentrations in saliva of thirteen term infants and fourteen premature infants. The infants were from 1 day to 8 weeks of age and the birth weights of the premature infants varied from 1,425 to 2,390 grams. The chloride concentrations are high at birth, drop rapidly during the first week of life, and then continue to fall very slowly. The abrupt postnatal fall is the same in both premature and term infants.

In Fig. 2 are presented the chloride concentrations in saliva of forty-six children varying in age from 2 months to 10 years. The chloride concentration continues to fall at a slow rate until about 2 years of age, where it appears to stabilize up to the age of 10.

Sixty-four sweat collections were made in the nursery. Of these, forty-six were arbitrarily discarded because the amount of sweat was less than 150 mg. The remaining eighteen included infants from 2 to 56 days of age, with birth weights from 1,350 to 3,800 grams. The chloride concentrations fall well within the range described for older children.[7]

DISCUSSION

The fall in chloride concentration in the saliva during infancy has been previously reported by Clemmens and collaborators as well as ourselves.[8] This parallels the experience with salivary sodium concentration.[9] The abrupt improvement in the ability to secrete a dilute saliva during the first week of life is demonstrated by both the newborn premature and term infant, indicating that this is an adjustment to extrauterine existence. After that the improvement is very gradual over a period of months and is probably related to the more gradual changes of growth and development.

This performance is reminiscent of the ability of the kidney to respond to a water load.[10] During the first few days of life the kidney does not diurese in response to a water load, but rapidly develops this capacity during the next few weeks. This is true of both the premature and term infant, being related to post-partum age rather than gestational age. The suggestion is made, however without evidence, that the adjustment may be endocrine in nature. A similar suggestion has been made regarding salivary function.[9] However, it is also possible that local stimuli following birth, for example, oral feeding, may be more significant.

The evidence relating the salivary chloride concentration to the presence of staphylococci in the nasopharyngeal flora is circumstantial. The staphylococcus is found with particularly high frequency among two groups of individuals with no other obvious similarity than their high salivary chlorides, namely, the patients with cystic fibrosis of the pancreas and newborn infants. Some support for this theory is gained from the observation that in vitro the staphylococcus is more resistant to high salt concentrations than other microorganisms.[3]

The measurements of chloride concentrations in sweat gave totally different results. Previous publications gave the results on normal children

1½ years of age and older.[7] Di Sant-'Agnese has since observed that infants as young as 7 weeks are capable of secreting a dilute sweat.[11] It now appears that this function is well developed even in the premature infant. The many determinations that had to be discarded because of inadequate collections merely confirm the well-known fact that the premature infant does not sweat much.[12]

Since the chloride concentration in saliva and sweat are used in the diagnosis of cystic fibrosis of the pancreas, it is worth stressing that elevated salivary chlorides in early infancy must be interpreted with caution. On the other hand, an increased chloride concentration in sweat may be considered significant even at birth.

SUMMARY

1. The chloride concentration of the saliva at birth is high in both premature and term infants and falls rapidly during the first week of life.

2. The salivary chloride concentration continues to fall at a much slower rate during the first two years of life and then appears to stabilize through 10 years of age.

3. On the other hand, the chloride concentration of sweat is low at birth, even in the premature infant.

4. The importance of these observations in the diagnosis of cystic fibrosis of the pancreas is pointed out.

5. The possible relation of salivary chloride concentration to the presence of the staphylococcus in the nose and throat is discussed.

We are indebted to Miss Ada McLaughlin, R.N., and her nursing staff for the sweat collections in the premature unit.

REFERENCES

1. McGrady, K., and Bessman, S. P.: The Detection of Mucoviscidosis by the Determination of Saliva Chloride, A. M. A. Am. J. Dis. Child. **90:** 610, 1955.
2. Di Sant'Agnese, P. A., and Andersen, D. H.: Celiac Syndrome. IV. Chemotherapy in Infections of the Respiratory Tract Associated With Cystic Fibrosis of the Pancreas, Am. J. Dis. Child. **72:** 17, 1946.
3. Knight, V.: Fibrocystic Disease of the Pancreas, 18th Ross Pediatric Conference, Iowa City, Sept. 30, 1955, p. 70.
4. Torrey, J. C., and Reese, M. K.: Initial Aerobic Flora of Newborn (Premature) Infants, Am. J. Dis. Child. **67:** 89, 1944. Torrey, J. C., and Reese, M. K.: Initial Aerobic Flora of Newborn Infants, Am. J. Dis. Child. **69:** 208, 1945.
5. Schales, V., and Schales, S. S.: Simple and Accurate Method for Determination of Chloride in Biological Fluids, J. Biol. Chem. **140:** 879, 1941.
6. Schwachman, H., Leubner, H., and Catzel, P.: Mucoviscidosis, Advances Ped. **7:** 249, 1955.
7. Di Sant'Agnese, P. A., Darling, R. C., Perera, G. A., and Shea, E.: Abnormal Electrolyte Composition of Sweat in Cystic Fibrosis of the Pancreas, Pediatrics **12:** 549, 1953.
8. Clemmens, R. L., Ivins, I., and Bessman, S. P.: Saliva Chloride in the First Year of Life, presented before the Society for Pediatric Research, May 7, 1956, Buck Hill Falls, Pa.
   Dancis, J., Grobow, E., and Boyer, A.: The Effect of Age on the Chloride Concentration of Saliva, presented before the Society for Pediatric Research, May 7, 1956, Buck Hill Falls, Pa.
9. Prader, A., and Gautier, E.: Die Na- und K-konzentration in gemischten Speichel, Helvet. paediat. acta **10:** 29, 1955.
10. Ames, R. G.: Urinary Water Excretion and Neurohypophysial Function in Full Term and Premature Infants Shortly After Birth, Pediatrics **12:** 272, 1953.
11. Di Sant'Agnese, P. A.: Personal communications, 1956.
12. Levine, S. Z., and Gordon, H. H.: Physiologic Handicaps of the Premature Infant, Am. J. Dis. Child. **64:** 274, 1942.

HYPERKINETIC BEHAVIOR SYNDROME IN CHILDREN

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THE "organic behavior syndrome" in children and the value of amphetamine in its treatment were first emphasized by Bradley.[1, 2] On the basis of recent clinical experience and study at the Emma Pendleton Bradley Home, both neurophysiologic and clinical facets of this syndrome are presented. It will henceforth be referred to as the "hyperkinetic impulse disorder."

It must be emphasized that most of our patients had normal intelligence. In some, the hyperkinetic impulse disorder was associated with some other of the "syndromes of cerebral malfunction," such as mental retardation of organic origin, cerebral palsy, epilepsy, and various sensory-motor handicaps.

SYMPTOMS

The essential symptoms of the hyperkinetic impulse disorder are the following:

Hyperactivity.—The children show involuntary and constant overactivity which greatly surpasses the normal. This may already be present during early infancy. Motor development is often advanced, and histories frequently indicate that the child climbed out of the crib well before a year of age. Parents often say such things as that he walked early and there was "no holding him" after that, or that he could not be kept in a play pen and was into everything, having to be tied to keep him in the yard.

On the other hand, the hyperactivity may not be noted until later, anywhere up to 6 years of age. Descriptions by parents as to these later phases may include comments to the effect that this child never walks, but always runs, or that he is always on the go and never sits still, even for television! It is quite common to hear that the child cannot sit still even to eat, running in and out for a mouthful at a time. The teacher complains that the child cannot stay in his seat or stay in line for assembly.

Short Attention Span and Poor Powers of Concentration.—Concentration on a single activity is usually short, with frequent shifting from one activity to another. This is especially noticeable at school. One hears statements such as: "The child never sticks to anything very long. He picks up something, drops it, goes on to something else. If he has ten examples in a test, he finishes only four. He is always paying attention to someone else's work in school."

Variability.—Behavior is unpredictable, with wide fluctuations in performance: "You can never tell which way the cat is going to jump. Sometimes he is good, sometimes bad." Grades in school may be variable also.

From the Emma Pendleton Bradley Home.

Impulsiveness and Inability to Delay Gratification.—The child is described as doing things on the spur of the moment, without thinking. He also seems unable to tolerate any delay in gratification of his needs and demands.

Irritability.—Frustration tolerance is much lowered. Fits of anger are easily provoked.

Explosiveness.—This r e a l l y is a compound of the preceding two, or possibly three, items. The reactions of these children are often almost volcanic in their intensity.

Poor School Work.—The previously described behavior disturbances make it difficult for a child to participate successfully in his school work. In addition, there is often some specific learning difficulty, particularly in arithmetic. It seems to be a compound of problems in the visuo-motor-perception and concentration areas. Reading problems and reversals in reading and writing are also frequent. The handwriting is often crabbed, irregular, or otherwise poor.

AGE DIFFERENCES

The initial diagnosis is often difficult because of the variability in the time of appearance of behavioral signs. Generally one or more of the above symptoms appear and become a focus of primary concern of the parents.

Infancy.—Reviews of histories show that in early infancy there are a number of clues for diagnosis. The baby may have been exceedingly irritable and cried readily or he may have been unusually placid and quiet. Often, he may have been exceedingly active and may have had an advanced developmental schedule.

Preschool.—Sometimes no abnormal behavior is observed till the youngster begins to walk. He may then seem to burst into an ever-widening circle of activity.

School Age.—Often there is no complaint from the family until 5 or 6 years of age when the child enters school. The problem may either appear then or be first recognized and dramatized by the reaction of the teacher.

In later years this syndrome tends to wane spontaneously and disappear. We have not seen it persist in those patients whom we have followed to adult life. The age of our oldest patient with the syndrome is 18 years. The time of disappearance for the individual child, however, seems impossible to predict. It may disappear at any age from 8 to 18.

SEX AND ORDINAL DIFFERENCES

This syndrome is more frequent in males than in females and in first-born than in subsequent children.

SLEEP DISTURBANCES

It has frequently been observed that, in the present permissive era of child management, the previously common feeding problems have been replaced to a large extent by sleeping problems.[3] Not all of these are due to mismanagement, however. Sometimes they are associated with the hyperkinetic syndrome.

In some instances hyperactivity increases at bedtime, with difficulty in falling asleep. More often, the child falls asleep at the proper time but wakens after a few hours. A variety of "misdemeanors" may follow, ranging from vocalizing in bed to turning on the lights and rampaging through

the house in hyperactive, noisy, and sleep-disturbing play. On some occasions both the early and the late types of sleep disturbance occur in the same child. Study usually shows the classical hyperkinetic kind of behavior during the day also. Generally, the parents are so desperate over the night problems that the daytime ones pale in significance.

EMOTIONAL DISTURBANCES

The hyperkinetic syndrome often leads to emotional disturbances in a variety of ways, which were outlined in a previous paper.[4]

Infancy.—Freud and subsequent writers have emphasized that the newborn infant operates under a homeostatic principle which induces great discomfort when any tension (such as hunger, etc.) accumulates, with a great need to discharge this tension and return to the previously undisturbed state. Prompt and consistent relief of these tensions results in a happy and satisfied baby. He or she soon comes to expect that needs will be met and tension relieved. They tend to develop relatively happy, confident orientations toward future life. Conversely, Spitz,[5] Goldfarb,[6] and others have shown that infants who did not have a relatively abundant and flexible kind of mothering have their tensions relatively unrelieved. They in turn tend to grow up to be tense, unhappily expectant individuals. They seem to represent a bottomless, overdemanding, and never-satisfied pit of insatiable wants and requirements, resulting in great unhappiness for themselves and others.

The previous paper[4] gave the basis for believing that underlying the hyperkinetic syndrome is injury to or dysfunction of the diencephalon, making the individual unusually sensitive to stimuli flooding in from both peripheral receptors and viscera. Such a state could well make a young infant respond with greater than usual urgency to an otherwise normal amount of tension coming from the usual organic sources (hunger, full bladder, coldness, etc.). Frequently, these infants are hypertonic, querulous, irritable. They may cry loud and long, squirm about restlessly, seem tense, demanding, and unsatisfied. Many of these manifestations are dismissed as "colic."

Infants may react to failure to relieve tension as they do to extreme deprivation. Thus, in an infant with the hyperkinetic syndrome, a normal amount of mothering may actually be inadequate. This presents the paradox of an apparently normal and quite adequate mother, who may previously have reared healthy and happy children but who now, inexplicably, depite her best endeavor, has a tense, chronically unhappy, and demanding child.

This may explain the hypothesis suggested by Greenacre in her book *Trauma, Growth and Personality.*[7] Her observations and speculation led her to conclude that accidents at birth may have much to do with the specific form and pattern of anxiety reaction and with the ability to sustain anxiety in developing individuals and thus have a basic role in determining their personality attributes.

Many new mothers have a deep and often unconscious, but sometimes conscious, concern about their own worth and adequacy as females, as wives, and as mothers. An infant who behaves in the way just described seems to

them to offer clear proof of their unfitness. This leads to further tension in the mother and increasingly frantic efforts to mold the child into a more acceptable pattern. As these attempts are usually unsuccessful, an unconscious hostility toward the child, to which in turn the infant responds, may set off a train of secondary emotional disturbance.

School Age.—In some instances the hyperkinetic behavior syndrome is not manifest in the early months of life but appears anywhere up to 6 years. These individuals, though spared the infantile types of disturbance, may yet fall prey to others.

The various components of the hyperkinetic syndrome, when found in the child of school age, try the patience of the parents severely. Such a child does not fit into any scheme of family activity. The peculiar, impulsive, and almost explosive responses are particularly intolerable to many parents who find it difficult to accept from their children behavior which has an aggressive component.

Such children may be beyond the ability of the teacher to tolerate. With forty-five to fifty children in a classroom, it can be unbearably disruptive to have among them a child who, despite seemingly good intelligence, cannot sit still, cannot keep his mind on his work, minds other pupils' business instead of his own, hardly ever finishes the work assigned, and yet, unpredictably, may turn in a perfect paper. As a result, the teacher tends to put increased pressure upon the child to conform and to live up to apparent capabilities. Since he is unable to comply, strife and unhappiness result.

In addition, the specific learning difficulties, usually in arithmetic but frequently in reading, as well, combine with the child's increasing unhappiness to make for school failure. Since this picture is frequently present from the very beginning of school, the child generally fails to gain a proper foundation in the fundamentals upon which all subsequent schooling depends, so the situation becomes worse and worse.

To these psychologic stresses are added the generally unhappy situation at home, with more and more forceful expression of their unhappiness by parents, who cannot understand why they have been afflicted with so uncooperative, resistant, and difficult a child.

The net result is unhappiness in a child whose image of himself is a distorted and unfavorable one. He may react with almost any kind of habit or conduct disturbances, such as temper tantrums, masturbation, thumbsucking, ties, stealing, assault, truancy, withdrawal, etc. A few of these children may eventually develop the type of symptom complex formerly called "psychopathic behavior with emotional instability."

It is significant that the behavior accompanying the situations just described is generally not of a neurotic nature (anxiety reaction, phobias, obsessions, etc.), but rather of the "acting-out variety" (stealing, excessive eating, destructiveness, etc.). However, the presence of the hyperkinetic syndrome offers no immunity against the development of neuroses due to the usual causes, particularly since there may be ego weaknesses associated with the syndrome. These ego weaknesses may include difficulties in perception, in motor control, in ability to inhibit and redirect impulses and to withstand stresses. In other words, it is possible to have both the

hyperkinetic syndrome and a neurotic state in the same individual but due to different causes, with the hyperkinetic syndrome not being responsible for the development of the neurotic picture.

MECHANISM

In a previous paper[4] we gave the reasons for believing that this syndrome results from injury to or dysfunction of the diencephalon in early life. The result is an undue sensitivity of the central nervous system to stimuli constantly pouring in from peripheral receptors and from viscera. The diencephalon may also be released to some extent from the moderating control that results from the characteristic interplay between cortex and diencephalon. The resulting components of sensitivity and forced responsiveness to stimuli, inability to inhibit and delay responses, and visuo-motor difficulties—all combine to produce the characteristics of the hyperkinetic syndrome.

ETIOLOGY

Apparently anything which produces dysfunction of the diencephalon and the diencephalocortical interrelations before birth, during birth, or in the first five years of life may result in this syndrome. Many of the factors which are responsible for cerebral palsy can produce the syndrome.[8]

The hyperkinetic syndrome is often found in epileptic children, as pointed out by Bradley.[10, 11] The medications used for controlling the epileptic manifestations do not generally alter the behavior, though they may suppress the seizures.

CONCOMITANT PHENOMENA

Brain injury, due to one of the causes listed above, is not always precisely limited to the region of the diencephalon. Frequently there is concomitant injury to other subcortical areas, to cortex, cerebellum, etc. This may result in other syndromes of cerebral malfunction, such as cerebral palsy, neurological blindness or deafness, or mental retardation. Thus, maldevelopment, injury, or anoxia before birth, during birth, or in the early years of life may result in symptoms in the neurological, the intellectual, or the behavioral spheres, or in any combination of these.

It is common to find the hyperkinetic syndrome in children who are retarded on an organic basis. It is also often associated with cerebral palsy, even as much as 23 per cent.[12] However, each of these sequelae to injury may occur alone. The majority of our patients with the hyperkinetic syndrome have been of normal intelligence.

DIAGNOSIS

The history has been the most valuable item in making the diagnosis, in two ways. The first is to provide evidence of the possible etiological items, such as high forceps delivery or severe pertussis in infancy. The other significant aspect has been in the parents' description of the characteristic syndrome in their child.

NEUROLOGICAL EXAMINATION

In children with only the behavior disorder and without concomitant neuromotor abnormality and mental retardation, the standard neurological examination generally shows no consistent abnormality. There may be scattered reflex changes or cranial nerve abnormalities, such as internal strabismus or central facial weakness. These are neither consistently nor frequently present.

As part of the neurological examination, it has been a custom to draw, before the child, on unruled white paper, four geometrical figures, in the following order: square, circle, cross (with equal and equidistant arms), and diamond. Allowing for the age factor (a child must be 7 years old, mentally, before being able to copy the diamond), there is generally and characteristically a distortion of these figures by the brain-injured child. This has been one of the most consistent and helpful signs of this condition. (Fig. 1.)

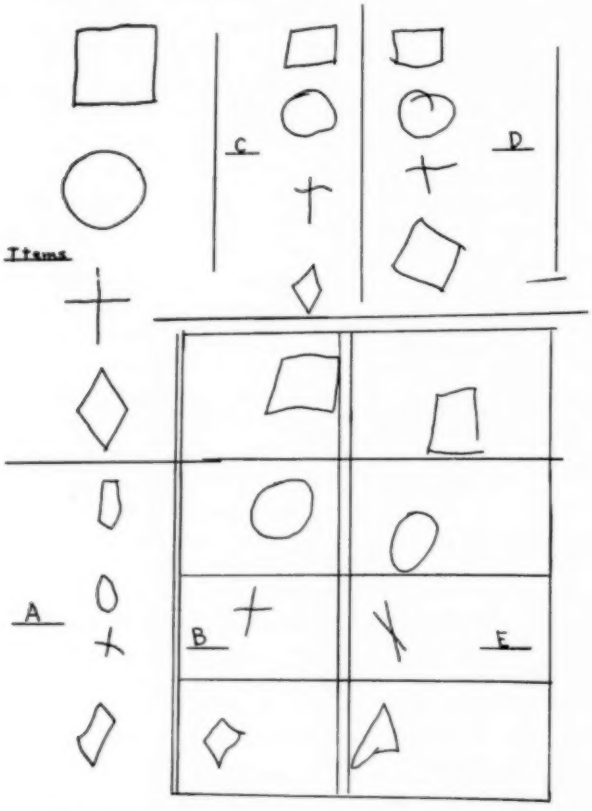

Fig. 1.—Distortions of geometric figures. Upper left-hand column shows items as presented to child for copying. The succeeding columns show typical distortions produced by children with the hyperkinetic syndrome (all being over 7 years of age).

ELECTROENCEPHALOGRAM (EEG)

Many authors[13-16] have commented on the fact that children with disturbed behavior show a greater incidence of abnormal electroencephalograms (EEG's) than do a control group. The abnormalities are nonspecific. They include abnormally fast or slow activity, both generalized and localized, amplitude asymmetries and paroxysmal seizure discharges, both generalized and localized. It is our impression that these abnormal EEG's reflect the presence of a large number

of children with the hyperkinetic syndrome. These EEG's are probably traumatically, and not genetically, determined. They are similar to those found in a large group of children with cerebral palsy. However, there is no close correspondence between EEG and abnormality. Many of the children in this series with well-marked symptoms of the hyperkinetic syndrome have had normal EEG's. Conversely, a number of the children without the hyperkinetic syndrome have had abnormal EEG's.

The EEG is actually a cortical record, though influenced by subcortical centers. Many of the abnormal EEG's therefore indicate the presence of cortical damage. This probably is often concomitant with subcortical damage from the same insult, and in this case there could be hyperkinetic behavior along with the abnormal EEG. If the cortical damage were not associated with subcortical damage, there could result an abnormal EEG without the simultaneous presence of the hyperkinetic syndrome.

An alternative explanation is suggested by the English authors under the influence of Hill and Walter.[17] They point out the frequent presence of an unusual degree of "theta rhythm" or 6 to 7 per second activity in both parietal regions in children with disturbed behavior, and unilaterally in older individuals diagnosed as psychopaths. They suggest that this represents delay in maturation and in the establishment of normal corticobasal relations.

Photo-Metrazol Threshold.—In a previous paper[18] we have shown how the technique of Gastaut[19] may be adapted for use with children. This consists of administering Metrazol intravenously in a standardized way while simultaneously stimulating the patient by flashes of light from a powerful stroboscope, at a set frequency. The end point is indicated by the appearance of a specific discharge in the electroencephalogram. It is recorded as the "photo-Metrazol threshold," or the amount of Metrazol, in milligrams per kilogram of body weight, required to evoke this specific response. A low threshold is thought to reflect diencephalic dysfunction.

In these studies, for children between 7 and 12 years, the following range of photo-Metrazol thresholds was found (in milligrams of Metrazol per kilogram of body weight):

Normal	6.5 and above
Borderline abnormal	5.1 to 6.4
Abnormal	Less than 5.1

These studies showed a marked and statistically significant difference between hyperkinetic and nonhyperkinetic patients. Although all were emotionally disturbed, the nonhyperkinetic group were thought to have no significant organic factors. Of those with hyperkinetic behavior only 18 per cent had a threshold above 6.5 mg. per kilogram, while of those without hyperkinetic behavior, 66 per cent had a threshold above 6.5 mg. per kilogram.

Correspondingly, a striking difference is seen when both groups are compared on the basis of *low* threshold. The children demonstrating hyperkinetic behavior had thresholds of 5.0 mg. per kilogram and below in 59 per cent of the cases. This was true for only 5 per cent of the children who did not manifest hyperkinetic behavior, though they were emotionally disturbed.

The photo-Metrazol test is helpful in the diagnosis of the hyperkinetic syndrome. The lower the threshold was

below 6.5 mg. per kilogram, the more likely the diagnosis. The test is difficult to perform and only recently is coming to have clinical value.

A wide variety of determinations, such as blood sugar, blood urea, and nonprotein nitrogen, cholesterol, cephalin flocculation, and other tests, have been studied in these children during the past eight years. There has been no positive correlation with the hyperkinetic syndrome.

PSYCHOLOGIC TESTS

Certain general statements may be made regarding the use of these tests in the diagnosis of the hyperkinetic syndrome. One important finding has been the appearance of signs usually associated with brain dysfunction, but with a lack of consistency of such findings within the total battery. In almost every case involving the hyperkinetic syndrome, there are disturbances on tasks involving visual motor function. Signs of brain damage usually associated with cortical involvement, such as perseveration, concretization, impotence, and oversimplification, do not usually occur except in those cases with cortical damage in addition to midbrain defect.

The differentiating characteristics of these records involve errors in perceptual-motor function and/or conceptualization consistent with either retarded perceptual-motor development or impulsivity in thinking and action.

DIAGNOSTO-THERAPEUTIC TRIAL

In our experience amphetamine is a specific for the treatment of the hyperkinetic syndrome. It is ineffective in other conditions. This clinical observation is supported by the highly specific effect of amphetamine upon the abnormally low photo-Metrazol threshold, raising it to a normal level simultaneous with clinical improvement.[4]

A therapeutic trial of amphetamine may be used as a diagnostic test as well. A favorable response to amphetamine is supportive evidence for a diagnosis of the hyperkinetic syndrome.

BARBITURATE REACTION

Phenobarbital or other barbiturates are ineffective in the hyperkinetic syndrome. Instead the great majority of children with this syndrome react adversely to such medication. They often become more irritable, unmanageable, and active. This reaction is so marked as almost to provide a specific diagnostic test in itself.

TREATMENT

Amphetamine.[1, 20]—

Favorable Effects: The favorable effects of amphetamine are to counteract the symptoms of the hyperkinetic syndrome. Most striking is the child's newly found ability to maintain his attention on things for longer periods. He is less driven in his behavior and in general easier to get along with. The result may be dramatic and result in a complete alteration in the child's behavior and in the parents' and teachers' attitudes toward him.

Sometimes, if too high a dosage is given, the counteraction of the syndrome may go to the extreme of "freezing the patient" or fixating him to what he is doing, and may even put him to sleep.

Unfavorable Effects: The unfavorable effects do not generally require discontinuance of the medication. Parents should be warned in advance. For the first two or three nights the child may have difficulty in falling

asleep. The appetite is often reduced at first but usually improves spontaneously in a few weeks. In some instances the anorexia persists.

The parents should also be told about the "amphetamine look"—a pale, pinched, serious facial expression with dark hollows under the eyes. It is of no serious consequence but the parents must be prepared for adverse comment concerning the child's appearance.

There is another group of unfavorable effects which, unlike the first, generally require discontinuance of the medication. First among these is an increase in components of the hyperkinetic syndrome, including increased hyperactivity, irritability, and easy tears. In this same group also are complaints of headache, epigastric distress, and tremor of the fingers. There is reason to believe that this group of children are either extremely sensitive to the drug, or their current behavior primarily is not the result of organicity.

Duration and Time Factors: When amphetamine is given immediately after breakfast, in tablet or liquid form, the effect is generally apparent and marked within twenty minutes. It starts to fade by noon, and is usually gone by 6 P.M.

There is generally no carry-over effect. Regardless of the results on the day on which given, nothing will usually be noted the following day if the medication is not repeated. Doses given later in the day of course have a similar span of action. Children with sleep disturbances of the hyperkinetic type may require a nighttime dose of amphetamine.

The syndrome tends to clear spontaneously by the time adulthood is reached and usually before this. The particular time of this change is unpredictable in the individual case. Therefore it has been our custom to continue the medication, through the year and to omit it for a brief period during the summer. If the hyperkinetic syndrome is still present, this is quickly apparent and the medication is resumed for another year. The medication has been continued in this way for as long as six years.

Specificity of Medication: There is generally a quite sharp specificity of action of the two forms of amphetamine currently available, dextro-amphetamine* and racemic amphetamine.† It is common to find in a particular individual that one of these forms may have either no effect or unfavorable effect, while the other form has beneficial results. Or both may have favorable effects, but one more so than the other. It has therefore been our rule to try both forms for each individual.

Available Forms: Racemic amphetamine is available as 5 and 10 mg. tablets and 10 mg. long-acting capsules. Dextro-amphetamine is available in more variety. It may be used as 5 mg. tablets or in liquid form as an elixir, one teaspoon containing 5 mg. It is also available as a long-acting capsule, in both 10 mg. and 15 mg. sizes which sometimes may be preferable. On occasion it has been helpful to combine the short and long-acting forms.

Dosage: This is highly individual. For children under 6 years of age we begin with 5 mg. of racemic amphetamine or 2.5 mg. of dextro-amphetamine each morning after breakfast

*Supplied as Dexedrine sulfate by Smith, Kline & French.

†Supplied as Benzedrine sulfate by Smith, Kline & French.

for one week. If the results are not adequate, the dose is raised to 10 mg. of racemic amphetamine or 5 mg. of dextro-amphetamine daily after breakfast for one week.

For children over 6 years the above figures are doubled—starting with 5 mg. of dextro-amphetamine or 10 mg. of racemic amphetamine and going to 10 mg. of dextro-amphetamine or 20 mg. of racemic amphetamine.

As previously indicated, both forms of medication are tried in each case, to see which would be the more efficacious, and the dosage then stabilized.

Sometimes neither form, in the dosages just mentioned, gave any beneficial effect. On the other hand, no adverse effect was noted either. In such instances the dose was gradually raised to a level where either beneficial or toxic effects were noted. In our series the highest maintenance dose was 20 mg. of dextro-amphetamine or 30 mg. of racemic amphetamine daily.

In some cases the standard after-breakfast dosage was not sufficient and it was necessary to add medication immediately upon rising or at noon or at 3 or 4 P.M. Sometimes it was helpful to waken a child at 6 A.M. for the first dose. In cases of sleep disturbance, a dose after supper was sometimes necessary as well.

Habituation: In no case in our experience was there habituation in the drug addiction sense. Sometimes, as children grew older and larger, they required higher dosages of medication. Rarely, a particular medication which had previously been efficacious seemed to lose its effect. In these cases, switching from dextro-amphetamine to racemic amphetamine or vice versa seemed helpful.

Specificity: Amphetamine is highly specific for behavior disturbance associated with the hyperkinetic syndrome. It is ineffectual or has adverse effects in behavior disturbances without organic components.

Mental Retardation: In children with a mixture of the hyperkinetic syndrome and mental retardation amphetamine is helpful also. It must be emphasized to the parents that this medication will not confer upon the children any more intelligence than they already have. However, it often improves their functioning by removing the handicaps of the hyperkinetic syndrome, thus allowing them to focus their intelligence more efficiently.

*Chlorpromazine.**—Other authors[21] have reported favorably on the use of this medication in the hyperkinetic syndrome. We have found it helpful in individual cases. Its action is unpredictable, however. Some are helped by it and not by amphetamine. More are not helped by it but are by amphetamine. Some seem worse with it. In those cases the clinical impression here is that the specific entity of the syndrome is not altered and that the patients are reacting unfavorably to the soporific effects sometimes associated with use of chlorpromazine.

Considering the toxic potentialities of chlorpromazine, the fact that amphetamine more often seems efficacious and that treatment must often be continued for years, the amphetamines seem the agents of first choice. Chlorpromazine may serve well, however, for initiating treatment, particularly where parents are affected by adverse publicity concerning the use of amphetamines by juveniles, delinquents, etc. Then amphetamine may be tried later, first in combination and then alone.

*Supplied as Thorazine by Smith, Kline & French.

Rauwolfia Products.—Results with these medications have been more uncertain than with amphetamine or chlorpromazine. A few children have been helped, but most have shown either drowsiness or no favorable effect and a significant number have seemed to become worse. This may be related to current concepts that, in differing individuals and differing dosages, Rauwolfia products may either inhibit or stimulate the reticular activating system, a portion of the central nervous system which is probably concerned with the production of this picture.

Other Medications.—A variety of other medications have been advocated, such as Benadryl, Phenergan, Ritalin, Desoxyn, Miltown, Meratran, Dramamine and Bonamine, and Atarax. Our experience with these has been too limited for any valid statement as to their usefulness.

EDUCATION

The education of these children often requires ingenuity and many special measures adapted to their specific handicaps. Schoolteachers may be referred to the volumes by Strauss, Lehtinen, and Kephart[22] for guidance in these matters.

PSYCHOTHERAPY

The frequent presence of psychologic disturbances secondary to the hyperkinetic syndrome has already been mentioned. The possibility of concurrent hyperkinetic syndrome and independent psychologic disturbance, such as neurosis, has also been emphasized. When the hyperkinetic syndrome exists alone and is recognized early, there may be relatively minimal associated emotional disturbances. In these cases the favorable effect of amphetamine upon the behavior often induces an "era of good feeling" which has a beneficial psychologic effect.

Even here, a definite part of the treatment consists of work with the parents. They frequently manifest feelings of hostility toward the child and of guilt for this and for the role they fear they have played in creating the problem.

Often, the demonstration to the parents of an organic factor in the child's behavior leads to a great sense of relief concerning their own and the child's responsibility for the problem. They then are able to understand and accept the child's behavior more readily. If the physician in turn shows the parents that he understands and is not critical of them, he can help greatly to bring about a *rapprochement* between parents and child.

In many other cases, the situation is not so fortunate. In these, the problem has persisted long enough so that psychologic difficulties are of a much greater magnitude and persistence. In these cases psychotherapy with the child is needed. Medication and work with the parents do not suffice. In this sense, it is only for the early and milder cases that amphetamine may be regarded as a specific treatment. For the others, it may be regarded as a means of preparing the child for specific treatment, which in those cases is psychotherapy.

In a number of cases psychotherapy was indicated, but was unable to proceed or succeed unless the child was under the influence of amphetamine and thus able to simmer down and participate in the psychotherapeutic process.

Of course, for those presenting the mixture of hyperkinetic syndrome and

neurosis, specific psychotherapy is needed.

It would be unfortunate if, as a result of these observations, amphetamine were used indiscriminately for the treatment of behavior disturbance in children or if the need for specific psychotherapy were overlooked. Amphetamine has a specific role, but is no substitute for psychotherapy.

SUMMARY

A specific and common behavior disorder in children, the hyperkinetic syndrome, may be due to organic causes and is characterized by: hyperactivity; short attention span and poor powers of concentration; impulsiveness; irritability; explosiveness; variability; and poor school work.

A laboratory procedure, the photo-Metrazol EEG, offers a means of explaining the mechanism and confirming the existence of this syndrome.

It is often accompanied by emotional disturbances.

It responds to amphetamine and, to some extent, to other medications.

Psychologic guidance for the parents and psychotherapy for the children may be required.

It tends to disappear by the time adulthood has been reached.

REFERENCES

1. Bradley, C.: The Behavior of Children Receiving Benzedrine, Am. J. Psychiat. **94**: 577, 1937.
2. Rosenfeld, G. B., and Bradley, C.: Childhood Behavior Sequelae of Asphyxia in Infancy, Pediatrics **2**: 74, 1948.
3. Panel on Sleep Disturbances of Children, J. Am. Psychoanalyt. A. **4**: 514, 1956.
4. Laufer, M. W., Denhoff, E., and Solomons, G.: Hyperkinetic Impulse Disorder in Children's Behavior Problems, Psychosom. Med. **19**: 38, 1957.
5. Spitz, R.: Hospitalism, in The Psychoanalytic Study of the Child. I. New York, 1945, International University Press.
6. Goldfarb, W.: Effects of Psychological Deprivation in Infancy and Subsequent Stimulation, Am. J. Psychiat. **102**: 18, 1945.
7. Greenacre, P.: Trauma, Growth and Personality, New York, 1952, W. W. Norton & Co.
8. Denhoff, E., Smirnoff, V. H., and Holden, R. H.: Cerebral Palsy, New England J. Med. **245**: 728, 770, 1951.
9. Arey, J. B., and Dent, J.: Causes of Fetal and Neonatal Death, J. PEDIAT. **42**: 1, 205, 1953.
10. Bradley, C.: Treatment of Convulsive Child in Children's Psychiatric Hospital, Nerv. Child **6**: 76, 1947.
11. Bradley, C.: Behavior Disturbances in Epileptic Children, J. A. M. A. **146**: 436, 1951.
12. Denhoff, E., and Holden, R. H.: In Cruikshank, W. M., and Raus, George M. (eds.): Cerebral Palsy, Its Individual and Community Problems, Syracuse, N. Y., 1955, Syracuse University Press, chap. II, p. 57.
13. Jasper, H. H., Solomon, P., and Bradley, C.: Electroencephalographic Analyses of Behavior Problem Children, Am. J. Psychiat. **95**: 641, 1938.
14. Ellingson, R. J.: The Incidence of EEG Abnormality Among Patients With Mental Disorders of Apparently Nonorganic Origin: A Critical Review, Am. J. Psychiat. **111**: 263, 1954.
15. Jones, E., Bagchi, B. K., and Waggoner, R. W.: Focal Abnormalities of the Electroencephalogram in Juveniles With Behavior Disorder, J. Nerv. & Ment. Dis. **122**: 28, 1955.
16. Rabinovitch, R. D.: Juvenile Delinquency, Considerations of Etiology and Treatment, Pediatrics **17**: 939, 1956.
17. Hill, D., and Parr, G. (eds.): Electroencephalography, London, 1950, Macdonald, Ltd., chap. XI.
18. Laufer, M. W., Denhoff, E., and Rubin, E. Z.: Photo-Metrazol Activation in Children, Electroencephalog. & Clin. Neurophysiol. **6**: 1, 1954.
19. Gastaut, H.: Combined Photic and Metrazol Activation of the Brain, Electroencephalog. & Clin. Neurophysiol. **2**: 249, 1950.
20. Bradley, C.: Management of Behavior Problems in Children, M. Clin. North America **37**: 565, 1953.
21. Freed, H., and Peifer, C. A.: Treatment of Hyperkinetic Emotionally Disturbed Children With Prolonged Administration of Chlorpromazine, Am. J. Psychiat. **113**: 22, 1956.
22. Psychopathology and Education of the Brain Injured Child, vol. I by Strauss and Lehtinen, 1947; vol. II by Strauss and Kephart, 1955, New York and London, Grune and Stratton.

AGAMMAGLOBULINEMIA

Report of a Case

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SINCE the original description by Bruton[1] in 1952 of a case of agammaglobulinemia, several case reports of the condition in children and in adults, have been published. In all of these cases there was an extremely low gamma globulin level in the serum, while the other protein fractions were within normal limits. These patients suffered from repeated bacterial infections due to the absence of circulating antibodies in their serum. In children this syndrome is believed to represent a congenital defect, while in adults it is considered an acquired disease of unknown etiology. Several authors[1-4] have carried out immunological, biochemical, and hematological investigations and have demonstrated the immunological handicap in this syndrome. Recently Good and Zak[5] reviewed the condition in a comprehensive study of this "experiment of nature."

The serum of patients with agammaglobulinemia shows an absence of the gamma globulin fraction when examined by paper electrophoresis. Immunological studies, however, reveal minute quantities of gamma globulin in the serum. The level of gamma globulin is usually less than 30 mg. per 100 ml. plasma (normal, 600 to 1,000 mg.) and in a few patients has been as low as 4 mg. per 100 ml.[5, 6] The present report describes a case of agammaglobulinemia with typical clinical features. In this patient the gamma globulin level determined by immunological methods was lower than in any we could find reported in the literature.

CASE REPORT

The patient, a 5½-year-old boy, was born in Israel. His parents and a 2-year-old brother were in good health and no relevant data could be obtained from the family history. His father was born in Russia and has been in Israel for twenty-two years; the mother, of Moroccan extraction, was born in Israel. The child was vaccinated against diphtheria and typhoid and against smallpox, the latter leaving a large but normal scar. At the age of 1 year (May, 1952) he developed chicken pox, with an unusually prolonged course. The rash persisted over one month, with fresh crops occurring throughout this period, and was followed by a secondary infection of the skin which did not respond to penicillin but disappeared after Aureomycin therapy. At the age of 1½ years he suffered from diarrhea with a stool culture positive for paratyphoid C. Three months later (February, 1953) he was admitted for the first time to the Children's Department of the Hadassah University Hospital, Jerusalem, with meningitis. The culture of the cerebrospinal fluid revealed

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Diplococcus pneumoniae. He responded well to antibiotic therapy and made a quick recovery. Two months later he again had a severe attack of diarrhea, and on this occasion *Shigella sonnei* was cultured from the stool.

The child was seen again one year later (April, 1954) in the outpatient department. During the intervening period he had suffered from chronic cough with frequent periods of high temperature. The x-ray picture at this stage revealed opacities in the right lower lung field and signs of inflammation in the paranasal sinuses. These x-ray signs cleared up after antibiotic treatment. He continued to visit the outpatient department regularly because of repeated attacks of fever and cough. His general condition remained satisfactory and there were no significant physical findings. The absence of adenoid tissue in the nasopharynx was noted. Repeated blood counts showed a leukocytosis between 10,000 and 35,000, with a differential count within normal limits. A chronic bilateral suppurative otitis media developed during the following months with *Staphylococcus aureus* as the causative agent. In spite of intensive antibiotic treatment instituted in accordance with in vitro sensitivity tests, little improvement of the otitis media was noted. Repeated x-ray examinations of the lungs showed considerably increased hilar markings and shadows in the lower lung fields. The signs of sinusitis reappeared and the child suffered frequently from conjunctivitis, which was relieved by antibiotic eye drops.

At this stage the history of repeated infections, relieved only temporarily by antibiotics, aroused suspicion of impaired antibody formation, i.e., decrease of gamma globulin. The plasma protein examination by filter paper electrophoresis was accordingly done and revealed an absence of the gamma globulin fraction. Total proteins in the patient's serum were 5.1 per cent; albumin 3.7 per cent, and globulin 1.4 per cent. A complete absence of gamma globulin fraction on paper electrophoresis was found on repeated examinations. The values obtained are presented in Table I.

TABLE I

	PATIENT'S SERUM (PER CENT)	NORMAL (AVERAGE) (PER CENT)
Albumin	67.8	63
α_1-globulin	6.7	4
α_2-globulin	16.3	8
β-globulin	9.2	12
γ-globulin	0	13

Moving boundary electrophoresis performed on a Kern type apparatus confirmed the complete absence of the gamma globulin fraction.

Since April, 1955, the child has received intramuscular injections of 5 c.c. (800 mg.) gamma globulin every two weeks and his general condition has greatly improved. The attacks of fever have become less frequent and the cough has lessened. The purulent discharge from the left ear ceased, but there was no improvement of the right otitis media and therefore a mastoidectomy was performed. At operation a large quantity of purulent material was found in the mastoid cells and antrum, with osteomyelitis of the surrounding bone.

Two months after operation the purulent discharge from the right middle ear reappeared. It was relieved initially by antibiotics (Aureomycin), but has reappeared again at frequent intervals. It was noted that this aural discharge and occasional episodes of cough and coryza recurred shortly before an injection of gamma globulin was due. This deterioration was more marked if for some reason or other the interval between the injections of gamma globulin was prolonged for over two weeks. However, except for this chronic right otitis media and some mild respiratory infections, the child has been quite well during the last one and one-half years.

Immunological Studies.—The immunological examination was performed according to the technique by Wiener,[7] and based on the ability of antihuman globulin serum to agglutinate human red cells coated with Rh antibodies. Since human gamma globulin can inhibit this reaction, minute amounts of gamma globulin can be detected by performing this test in series of progressive dilutions of the serum in question. Applying this procedure, the amount of gamma globulin in the serum of our patient was 1/1,000 to 1/2,000 of normal, corresponding to a level between 0.5 and 1.0 mg. per 100 ml. plasma.

Further studies were carried out to demonstrate the postulated deficiency of antibody production. The child's blood group was A, and anti-B agglutinins were completely absent; the child's serum failed to agglutinate five samples of group B red cells. The Schick test was positive despite the previous vaccination against diphtheria. The child was again vaccinated with diphtheria and typhoid vaccine (two injections at an interval of two weeks). The serum was then examined at intervals of five days for two more weeks, and no antibodies appeared. The Widal test was negative in all dilutions to 1:320, beginning with 1:10, using H, O, and para-B antigen, and no diphtheria antibodies could be detected in the serum.

COMMENT

In most of the cases of agammaglobulinemia reported in the literature the serum was investigated by the electrophoretic method only, and a complete absence of the gamma globulin fraction was found. In a few cases, however, in which immunological studies were undertaken, minute amounts of gamma globulin were discovered.[5-7] In children in whom this defect appears to be congenital, the gamma globulin level is usually lower than in the acquired form seen in adults, and ranges in most of the cases between 4 and 30 mg. per cent.[6] Grant and Wallace have reported a case of agammaglobulinemia in an adult with an estimated gamma globulin level not exceeding 2 mg. per 100 ml. plasma. This was the lowest value recorded to date in the literature. In our patient the amount of gamma globulin was still lower ranging between 0.5 and 1 mg. per 100 ml. plasma.

Most of the reported patients with agammaglobulinemia, while prone to repeated bacterial infections, showed an apparently satisfactory resistance to most of the virus diseases. In children, as well as in adults, virus diseases follow the usual clinical course, with the apparent development of immunity. Good and Zak[5] studied the immunological response of their patients to virus antigens and were not able to demonstrate a more satisfactory antibody production to virus antigens than to bacterial antigens. No measurable antibodies appeared in their serum after repeated injection of influenza vaccine, spotted fever, Q fever, typhus and Western equine encephalitis antigen, and all three types of poliomyelitis virus. These authors concluded that either minute amount of antivirus antibodies, which could not be detected by the most delicate in vitro technique, can protect against virus infection, or that mechanisms other than those involving antibody production operate in the resistance to virus diseases. Our patient underwent an unusually prolonged varicella infection, with fresh eruption recurring during the course of one

month. However, smallpox vaccination did not, in his case, produce any unusual reaction, nor did he develop any other clinically diagnosed virus infection. Only one similar case of an unusual course of varicella was found recorded in the literature. Corbeel and associates[8] reported four cases of agammaglobulinemia, the first of which presented a nearly identical clinical picture of unusually prolonged varicella infection. The amount of gamma globulin in this patient's serum measured by electrophoretic method was stated as being absent. It is possible that the extremely low gamma globulin level in the serum of our patient was responsible for this unusual course of chicken pox.

With the institution of the treatment with intramuscular gamma globulin injections (5 c.c. every two weeks), there was a marked improvement in the child's condition, although the immunological study revealed only a slight increase in the gamma globulin level (up to 20 mg. per 100 ml. plasma). It was the impression that the dosage of gamma globulin was on the lower limit of the required amount, and a higher dosage was desirable. Most authors propose higher doses than we administered to our patient, but our supply of gamma globulin was limited, and only recently were we able to increase the dosage.

We have not observed a leukopenia in our patient, as described in some cases of agammaglobulinemia.[5, 9] The white blood count, was always high, and especially pronounced when an infection was present (35,000 during meningitis). We have also noted the characteristic absence of the adenoid tissues, as observed by Neuhauser.[10] Porter[11] has demonstrated that agammaglobulinemia is inherited as a sex-linked genetic trait through the mother. Elphinstone and co-workers[12] stated that congenital agammaglobulinemia has been reported only in persons of Northern European extraction. It is noteworthy that our patient's mother is of Moroccan extraction. There was no information of a similar case in the mother's family.

SUMMARY

A case of agammaglobulinemia in a 5½-year-old boy is presented. The gamma globulin level in the child's serum as determined by immunological method was extremely low, between 0.5 and 1 mg. per 100 ml. plasma, which is lower than in other cases reported in the literature. The child suffered from repeated bacterial infections and had experienced an unusually prolonged varicella infection. As patients with agammaglobulinemia usually show an apparently satisfactory resistance to the virus diseases, it may be postulated that in our case the extremely low gamma globulin level was responsible for the lack of resistance to chicken pox.

I wish to express thanks to Prof. J. Gurevitch and Dr. D. Nelken of the Department of Clinical Microbiology of the Hadassah Hebrew Medical School, Jerusalem, for the performance of the immunological and serological studies. The moving boundary electrophoresis was carried out by Mr. M. Breuer of the Weizmann Institute of Science, Rehovot, whose help is gratefully acknowledged. The mastoidectomy, as well as repeated ear, nose, and throat examinations, were performed by Dr. Z. Rosen of the Oto-Rhino-Laryngological Department of the Hadassah University Hospital, Jerusalem. A considerable quantity of gamma globulin for the treatment

of this patient was received as a gift from the Lederle Laboratories.

REFERENCES

1. Bruton, O. C.: Agammaglobulinemia, Pediatrics **9**: 722, 1952.
2. Grant, G. H., and Wallace, W. D.: Agammaglobulinaemia, Lancet **2**: 671, 1954.
3. Barandum, S., Büchler, H., and Hüssig, A.: Das Antikörpermangelsyndrom (Agammaglobulinämie), Schweiz. med. Wchnschr. **86**: 33, 1956.
4. Good, R. A.: Clinical Investigations in Patients With Agammaglobulinemia, J. Lab. & Clin. Med. **44**: 803, 1954.
5. Good, R. A., and Zak, S. J.: Disturbances in Gamma Globulin Synthesis as "Experiments of Nature," Pediatrics **18**: 109, 1956.
6. Gitlin, D.: Low Resistance to Infection. Relationship to Abnormalities in Gammaglobulin, Bull. New York Acad. Med. **31**: 359, 1955.
7. Wiener, A. S.: Serologic Test for Human Gamma Globulin, Am. J. Clin. Path. **25**: 595, 1955.
8. Corbeel, L., Lahey, E., and Guest, G. H.: l'Hypogammaglobulinémie chez l'enfant, Arch. franç. pédiat. **11**: 561, 1954.
9. Laski, B., Sass-Korstak, A., and Hillman, D. A.: Cyclic Neutropenia and Agammaglobulinemia, A. M. A. Am. J. Dis. Child. **88**: 820, 1954.
10. Neuhauser, H.: cited by Good, R. A., and Zak, S. J.[5]
11. Porter, H.: Congenital Agammaglobulinemia: A Sex-Linked Genetic Trait and Demonstration of Delayed Skin Sensitivity (abst.), A. M. A. Am. J. Dis. Child. **90**: 617, 1955.
12. Elphinstone, R. H., Wickes, J. G., and Anderson, A. B.: Familial Agammaglobulinaemia, Brit. M. J. **2**: 336, 1956.

The greatest care must be taken that he does not see terrifying pictures, nor should the one who has charge of him shew himself to him with a stern look on his face, lest he cause him fright, and so through depression and overmuch grieving he be ill affected and fall into bad ways and infirmities. For many have escaped illness simply through cheerfulness, and many through depression have become ill. Let the nurse always cheer the child with a bright and loving countenance when the child comes to her. For spirit transmitted through the glance of the eye can bewitch and make or mar so that it is no wonder that in a similar way diseases of mind and body can be given or taken away.

Let the child's guardian also have a care that in its presence, she does not herself utter or allow others to utter, blasphemies, curses or abuse or wicked or unchaste language, or anything which does not tend to the honour and reverence of God, lest he learn to say such things later to the great disgrace of his parents and often contrary to their views.

FROM OMNIBONUS FERRARIUS, 15-?

CUTANEOUS MONILIASIS IN A PREMATURE INFANT

Report of a Case With Unusual Clinical Manifestations

W. Harvey Cabaniss, Jr., M.D., Walter F. Manley, Jr., M.D., and Robert E. Swan, M.D.
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THIS communication describes the unusual occurrence of cutaneous moniliasis in a premature infant, beginning during the first week of life.

CASE REPORT

The patient, a Negro female, was admitted to the University of Virginia Hospital a few hours after her birth. An uncomplicated home delivery had been accomplished by a midwife. Gestation period was unknown. Pregnancy had apparently been uneventful although unsupervised. A single earlier pregnancy had terminated in abortion at about the fifth month. The health of the mother had been good.

At the time of admission to the hospital the infant was found to weigh 1,175 grams (2 pounds, 9½ ounces), but aside from prematurity she appeared to be in good condition. No skin lesions were noted. The child was placed in an Isolette and given the routine care accorded premature infants at this hospital, including 2.5 mg. vitamin K and 100,000 units procaine penicillin intramuscularly. The following day 25,000 units of penicillin-V was commenced by mouth every twelve hours, and this schedule was maintained for the ensuing fifty-four days. As is the practice at this hospital, a thorough cleansing of the skin with mineral oil was given three times a week, followed by application to the entire skin of bacitracin and neomycin in a water-miscible ointment base.

From the Department of Dermatology, University of Virginia School of Medicine.

On the second or third day of life a small, erythematous, moist, macular lesion was noted at the nape of the neck. The lesion was observed to enlarge peripherally during the following few days. Treatment was begun at that time with a hydrophilic ointment base containing 2,500 units bacitracin and 25 mg. neomycin per ounce. After two weeks of treatment no improvement was evident, and the opinion of a dermatologist was requested. The lesion was described on that occasion as being oval in configuration, annular in character, and measuring about 3.5 cm. in its greatest diameter. It appeared to originate in the posterior transverse fold of the neck, extending for the most part inferiorly. The lesion was mildly erythematous, with an elevated border which appeared moist but without gross vesiculation. The center was observed to be clearing, less red than the border, and covered with a fine, branny scale in moderate degree (Fig. 1). Examination of the remainder of the skin and of the mouth was not remarkable.

The lesion was scraped and a potassium hydroxide mount was prepared. Under the microscope, numerous small, oval, thin-walled, yeastlike cells were visible. Of particular interest, however, was the occurrence of fairly numerous unbranched chains of cells, apparently developing from incomplete separation of the budding elements. These filaments have been described as "pseudohyphae" and point strongly toward the presence of Candida organisms (Fig. 2).

Fig. 1.—Cutaneous moniliasis, showing lesion at nape of neck with raised, active border and clearing center. Patient is 33 days of age.

Fig. 2.—Potassium hydroxide mount prepared from lesion in Fig. 1 showing pseudohyphae. High power.

Culture on Sabouraud's glucose agar media of material removed from the lesion resulted in the appearance within forty-eight hours of moist, creamy colonies possessing a distinct yeastlike odor. Subculture on cornmeal agar was performed and the typical chlamydospores of *Candida albicans* were seen.

The patient's lesion was treated three times daily with a bismuth solution currently under clinical investigation by the Department of Pediatrics. After treatment with this preparation for nine days it was discontinued, for although it appeared to arrest spread of the lesion, significant local activity persisted. During this time, oral lesions on the mucous membranes typical of thrush were observed and treated successfully in a few days with the bismuth solution topically applied.

On the forty-second day of life, the lesion on the child's neck was substantially unchanged from the original description and treatment with a hydrophilic ointment containing one million units of nystatin per ounce was instituted. Applications were made four times daily, and by the end of the third day of treatment the lesion had practically disappeared. By the ninth day only slight residual hypopigmentation was evident. Medication was stopped at this time without recurrence of the lesion.

The child was discharged from the hospital on the sixty-second day of life, weighing 2,550 grams (5 pounds 10 ounces), and with no visible cutaneous abnormalities.

Culture of the patient's stool prior to discharge showed a massive growth of Candida sp. but chlamydospores were not seen. The mother was examined two weeks after the infant had been taken home, and at that time a moderate leukorrhea was found. Culture and potassium hydroxide mount of this secretion failed to demonstrate *C. albicans*.

DISCUSSION

Moniliasis, although common in infancy, usually manifests itself in such easily distinguishable forms as thrush or intertrigo. Onychia,[1] denuded patches on the skin,[2] or a generalized eruption[3] have been described as some of the more unusual variants of cutaneous moniliasis.

In several earlier reports[2, 4] lesions possessing distinct borders, with clearing centers suggestive of tinea corporis, have been described in children. The present case offers, first, an apparently unique instance of monilial infection closely simulating that caused by the superficial dermatophytes. Second, the onset in a patient less than one week of age is, insofar as can be determined, the earliest recorded appearance of moniliasis of cutaneous type. Holzel[5] has described "skin thrush" in the genitocrural area of a 2-week-old full-term infant, and Park and associates[1] have reported the occurrence of onychia in a 51-day-old premature infant.

The development of such a lesion as is presented in an infant only a few days old suggests that the infection may have been acquired via the maternal birth canal. A relatively high incidence, 28 per cent, of occurrence of *Candida albicans* in the vaginal tract of women in the third trimester of pregnancy has been reported.[6] In the same study maternal infection resulted in a thirty-five times greater chance of the child developing oral thrush than a baby born of a noninfected mother. In the present study *C. albicans* was not found in the vaginal secretions of the mother several

months post-partum. It is unfortunate that an earlier attempt at mycological studies of the mother could not have been made.

The possible influence of topical antibiotic therapy as a predisposing factor in development of the skin lesion is intriguing. Livingood and associates[7] have shown that following topical therapy with neomycin the prevalance of cutaneous moniliasis is increased. Such opportunity existed in this patient, as topical antibiotics were used regularly.

Prematurity, with its associated poor resistance to infection, may be an important factor in this case. It is interesting to note that although bacterial studies were not made, the rapid clinical response to nystatin tends to confirm the solitary role of *C. albicans* as the etiological agent.

SUMMARY

Occurrence of a lesion of cutaneous moniliasis of unusal type in a premature infant has been described. Mycologic studies confirmed the presence of *C. albicans* in the lesion, and prompt clinical response to nystatin topically applied substantiated the probability of *C. albicans* as the sole etiological agent.

REFERENCES

1. Park, D. R., Desmond, M. M., and Fahlberg, W. J.: Monilial Onychia: Report of a Case in a 51-Day-Old Premature Infant, J. PEDIAT. **44**: 313, 1954.
2. MacLeod, J. M. H.: Skin Disease Due to Monilia and Other Yeast-Like Fungi, Brit. J. Dermat. **42**: 549, 1930.
3. Strickler, A.: Generalized Cutaneous Monilial Infection, Am. J. Dis. Child. **68**: 382, 1944.
4. Winter, W. D., Jr.: Candida (Monilia) Infections in Children, Pediat. Clin. North America, pp. 151-161, Feb., 1955.
5. Holzel, A.: Skin Thrush in Early Infancy, Arch. Dis. Childhood **28**: 412, 1953.
6. Woodruff, P. W., and Hesseltine, H. C.: Relationship of Oral Thrush to Vaginal Mycosis and the Incidence of Each, Am. J. Obst. & Gynec. **36**: 467, 1938.
7. Livingood, C. S., Nilasena, S., King, W. C., Stevenson, R. A., and Mullins, J. F.: Pyogenic Infections Treated with Neomycin, J. A. M. A. **148**: 334, 1952.

PULMONARY MONILIASIS

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BIOCHEMICALLY, identical strains of *Candida albicans* vary enormously in virulence in man and in experimental animals.[1, 2] The fungus is often present in the mouths of individuals without any evidence of clinical infection. In debilitated subjects, gastrointestinal, urinary, and even generalized metastatic moniliasis has, in recent years, become a recognized serious complication of intensive wide-spectrum antibiotic therapy.[3] Also, in otherwise healthy people, oral or vaginal "thrush" is, of course, quite common. Primary pulmonary moniliasis is, however, not a commonly recognized clinical entity.[4, 5]

Castellani[1] described two cases of pulmonary moniliasis in 1905, and since then many cases apparently regarded as primary pulmonary lesions have been reported, especially in North America.[2, 4, 6] Pulmonary involvement complicating oral thrush in the newborn infant has also been described.[7] On the other hand, some question the concept of primary pulmonary moniliasis as a clinical entity, and regard the fungus involvement as secondary to an underlying pathology, especially tuberculosis, bronchiectasis, or neoplasm.[5]

However, there is little doubt that pulmonary infection by *C. albicans* is of immediate clinical importance regardless of whether it is primary or due to secondary invasion. A number of fatal cases ascribed to pulmonary moniliasis have been reported. Even though minimal, monilial infection of the lungs is capable of widespread destruction and fibrosis, with physically crippling end results.[2] The usual antibiotic therapy for tuberculosis, bronchiectasis, or pyogenic infections of the lung is not effective in preventing further tissue destruction by monilia unless accompanied by specific measures against the fungus. In fact, the treatment of the underlying condition may increase the spread of the monilia infection by destroying the bacterial flora and permitting more luxurious growth of the fungus.

The following case is reported because the condition is not commonly met in clinical practice, and because it illustrates, in at least this type of case, the necessity of directing immediate therapy primarily against the fungus, even though, as will be seen, the possibility of the existence of an underlying bronchiectatic lesion could not be definitely ruled out.

CASE REPORT

An 8-year-old mongolian male was admitted to the general pediatric service of the Bridgeport Hospital. The child presented a fever of 104° F., and a ten weeks' history of coughing, profuse night sweats, anorexia, and some loss of weight. The cough was generally more severe at night, usually unproductive, but at times he brought up mucopurulent material, which on

From the Bridgeport Hospital.

three occasions had been slightly blood stained. These symptoms had gradually increased in severity since their onset. During this period he had had three febrile episodes, was apparently seen each time by a different physician, "pneumonia" diagnosed, and the child given "a few shots" of penicillin. There was no family or social history of tuberculosis. The child had been subject to frequent "colds," but there was no previous history of any serious respiratory infection.

On examination, the child was feverish but did not appear unduly toxic.

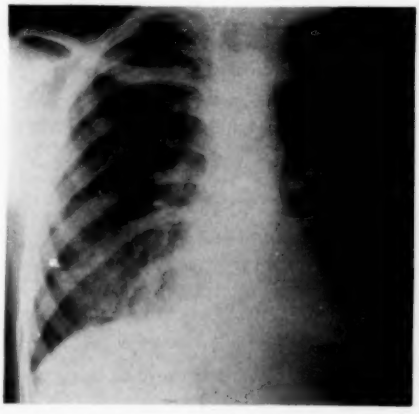

Fig. 1.—X-ray on admission. There is extensive mottled infiltration in the basal portion of both lungs. There is also a small cavity with a fluid level close to the left hilum.

There was no respiratory distress. The mucus membranes were rather pale and there was minimal bilateral impairment of the percussion note posteriorly over the lower half of the chest. Some crackling râles were also heard over the right base. Apart from the above signs and the characteristics of a mongolian physique, there were no other objective findings. There was no evidence of thrush infection in the mouth, nose, or pharynx. The child was admitted with a tentative diagnosis of bronchiectasis with acute exacerbation. The possibility of pulmonary tuberculosis was also entertained.

Blood examination revealed a total white cell count of 17,600 per cubic millimeter; differential—75 segmentals, 12 bands, 8 lymphocytes, 4 monocytes, 1 basophiles; hemoglobin, 11.9 grams per cent; and a sedimentation rate of 45 mm. per hour. A chest x-ray taken next morning (Fig. 1) showed "extensive mottled infiltration in the basal portions of both lungs. Also demonstrated was a small cavity with a fluid level apparently very close to the left hilum."

Intradermal tuberculin sensitivity tests were negative in two consecutive strengths. Repeated sputum specimen and gastric washings failed to show

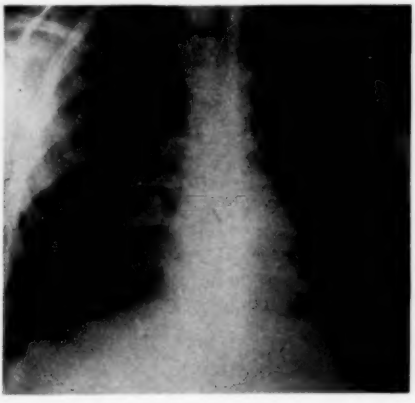

Fig. 2.—X-ray before discharge.

any acid-fast bacilli. The first sputum specimen gave a positive culture of *Hemophilus influenzae* and an abundant growth of *C. albicans*. A bronchoscopy was performed on the fourth day, and the material obtained from the bronchi gave a culture of *C. albicans*.

Treatment.—On admission the child had been started on penicillin therapy. This was discontinued four days later and the following regimen was instituted after a negative skin sensitivity test for monilia had been obtained: (1) potassium iodide, 2 grains three times a day; (2) Mycostatin, 40,000 units in 2 c.c. of aerosol by inhalations three times a day; (3) Mycostatin tablets, 500,000 units orally three times a day; and (4) postural drainage, three times a day of gradually increasing duration.

Progress.—The child showed gradual clinical and radiological improvement. An x-ray taken eighteen days after the institution of the above treatment showed only slight residual prominence of the lower lung markings; otherwise, lung fields were reported as being essentially clear. By this time the child was afebrile, very active in the ward, his appetite was good, and his cough had disappeared. He was discharged after six weeks, and at that time clinically and radiologically (Fig. 2), the chest was clear. No fungous growth was obtained from the sputum on five specimens.

It was decided not to perform a bronchogram at this stage but to follow the patient with bimonthly chest x-rays and clinical examinations. The child has since been seen on four occasions, and is well. The radiological appearance of the lung fields has stayed normal.

DISCUSSION

There is little doubt that neither tuberculosis nor pulmonary neoplasm was a primary or complicating factor in this case, and that pyogenic infection played only a minimal part. Mycostatin, derived from a culture of *Streptomyces noursei,* is effective only against yeastlike fungi and has no antibacterial action.[8] In view of the most gratifying response to Mycostatin and potassium iodide therapy, it is reasonable to assume that at the time the child came under our care, monilial infection was primarily responsible for his illness. It is further possible that initially the child might have had some upper respiratory infection of virus or bacterial etiology and the "few shots" of penicillin repeated at varying intervals were responsible for the relatively widespread pulmonary involvement by the fungus.

Pulmonary moniliasis has been treated in the past by the use of intravenous gentian violet, vaccines, quinine, etc., but the only effective results reported have been with prolonged (three to six months) therapy with potassium iodide,[2, 4] which has resulted in complete clinical cure in a certain percentage of cases. Mycostatin alone has also been effectively used.[7] Mycostatin has been used intravenously, but severe toxic reactions have been reported.[9] Mycostatin, when given orally, is not very well absorbed,[8] but is effective when given in conjunction with inhalations. In this case it is difficult to judge the relative part played by Mycostatin and potassium iodide. However, it is of interest that the duration of active treatment required in this case was shorter than that reported when potassium iodide alone has been used.[5]

SUMMARY

The literature regarding pulmonary moniliasis is briefly reviewed. A case of pulmonary moniliasis in an 8-year-old boy, who was treated effectively with the use of oral Mycostatin by inhalations, and oral potassium iodide, is reported.

This paper has been prepared with the assistance of the Pediatric Department of the Bridgeport Hospital. I would also like to thank my colleagues Dr. H. Austrian and Dr. W. McKenzie, who were responsible for the greater part of the care of this child.

REFERENCES

1. Castellani, A.: Arch. Dermat. u. Syph. **17**: 61, 1928.
2. Olbath, R. W., Donath, D. H., Johnston, H. G., and Kerr, W. J.: Ann. Int. Med. **35**: 97, 1951.
3. Dubos, J. R.: Bacterial and Mycotic Infections of Man, Philadelphia, 1952, J. B. Lippincott Co., p. 664.
4. Cohen, A. C.: Am. J. M. Sc. **226**: 16, 1953.
5. Robertson, D.: Edinburgh M. J. **55**: 274, 1948.
6. Flinn, J. W., Flinn, R. S., and Flinn, Z. M.: Ann. Int. Med. **9**: 42, 1935.
7. Beckmann, A. J., and Navarro, J. E.: J. PEDIAT. **46**: 581, 1955.
8. Year-book of Pediatrics, 1955-1956, Chicago, The Year Book Publishers, p. 98.
9. Editorial: J. A. M. A. **160**: 220, 1956.

INFANTILE CORTICAL HYPEROSTOSIS

Report of Case Misdiagnosed as Milk Allergy

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L. R., a 13-week-old white female, was first seen at our outpatient clinic on July 9, 1956, with the chief complaint of "a bump on the left side" for approximately four weeks.

Past history revealed a full-term, normal, spontaneous delivery of an 8 pound 7 ounce infant. The mother, 23 years of age, had an uneventful pregnancy and puerperium. The child began to smile at 6 weeks of age, and began to sit, propped up, at approximately 12 weeks of age. Until 9 weeks of age the infant was on a 1:1 evaporated milk formula without sugar. Cereal was started at 4 weeks, fruits at 6 weeks, orange juice at 8 weeks, and vegetables at 3 months. A pediatric vitamin preparation (0.6 c.c. every morning) was started at 2 weeks of age and continued to the present.

The child did very well until 7 weeks of age when, according to the parents, she began to cry continually and began spitting up her formula frequently. At 8 weeks of age she was taken to a civilian pediatrician who placed her on Nutramigen with no results. The child was then placed on whole cow's milk, also without results, and finally at 11 weeks of age she was placed on a soybean milk formula, with cessation of spitting up and crying within twenty-four hours, according to the parents. The father stated that he first noted the swelling of the left thorax at approximately 9 weeks of age and at this time the child appeared to be tender about the thorax when handled. This would coincide roughly with the onset of the symptoms of crying and spitting up. The swelling apparently increased during the next four weeks and the child was then brought to our outpatient clinic. At this time the child had been asymptomatic for approximately two weeks, and the only complaint was that the infant had "a bump on the side."

Physical examination revealed a well-developed, well-nourished, white female infant. Weight was 15 pounds 2 ounces; chest, 41 cm.; occipital frontal circumference, 41½ cm.; crown to heel, 65½ cm.; fontanel, flat; neck, supple; ear, nose, and throat, negative; heart, lungs, abdomen, and extremities, negative. The only positive physical finding was a bony protuberance over the area of the tenth left rib at the posterior axillary line. The skin was freely movable over the lesion and there was no tenderness, soft tissue induration, or erythema. The mass was firmly attached to the underlying rib. Laboratory work-up was as follows: white-blood cells, 11,100; differential, 57 per cent neutrophils, 42 per cent lymphocytes; red blood cells, 4,100,000; hemoglobin, 12.7 grams; hematocrit, 34 per cent; sedimentation rate, 13 mm. (uncorrected). Chest x-ray revealed irregular cortical thickening of the left tenth and eleventh ribs (Figs. 1 and 2). A complete roentgenological bone survey disclosed no further evidence of cortical hyperostosis in any of the other bones, including the mandible and clavicles.

It was felt at this time that the child had infantile cortical hyperostosis and that the illness diagnosed as milk intolerance or allergy was actually the active stage of the disease with

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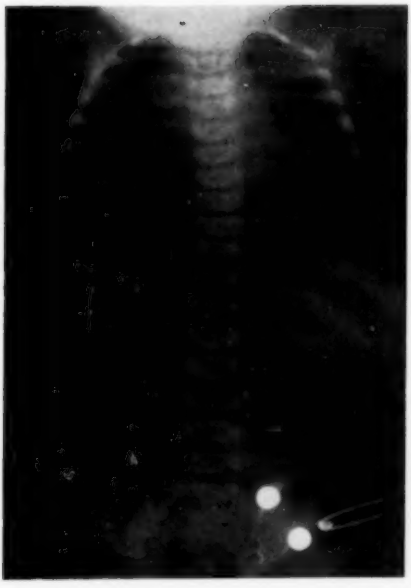

Fig. 1.—At time of first visit, at age 13 weeks.

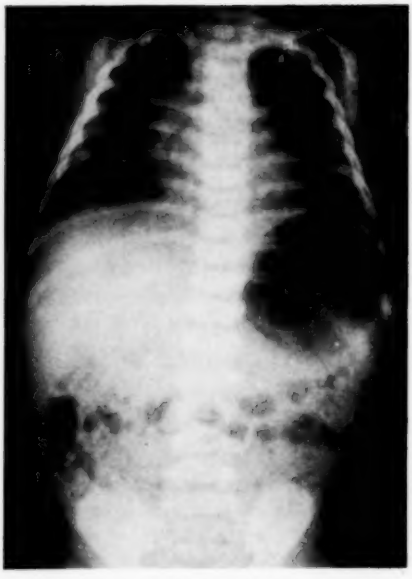

Fig. 2—One week later, at age 14 weeks.

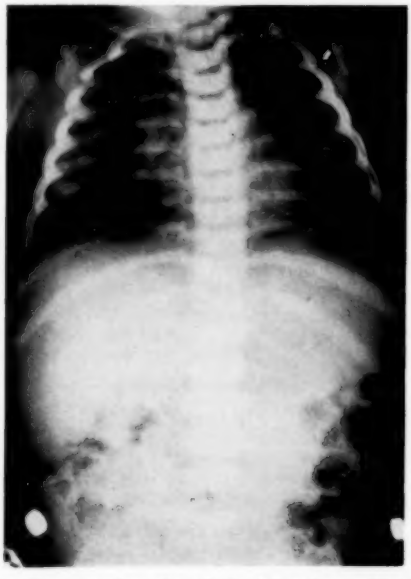

Fig. 3.—Two months after first visit, at age 22 weeks.

systemic symptoms of hyperirritability. Accordingly, the child was placed on a 1:1 evaporated milk formula, no sugar, in order to test the validity of this conclusion. The child has had no recurrence of the previous symptoms, diagnosed as milk allergy, and has been contented on the evaporated milk formula. The mass has been steadily decreasing in size, according to both palpation and x-ray examination, since the child's first visit (Fig. 3).

DISCUSSION

This particular case is both interesting and instructive, since the condition was diagnosed as milk allergy and the child apparently responded well to soybean milk. The failure of the previous clinical picture to return when the child was again placed on evaporated cow's milk leaves little doubt that the previous symptoms were not due to milk allergy and that the "cure" was coincidental. Whether or not there was involvement of bones other than the tenth and eleventh ribs (left) we do not know; however, during the length of time the child has been under our observation there has been no evidence of further involvement, and the condition has been asymptomatic and rapidly regressing.

Infantile cortical hyperostosis (Caffey's disease) is characterized by localized enlargement of various bones, most commonly the mandible and clavicles, but also the calvarium, ribs, scapulas, metatarsals, and long bones of the extremities, due to a hyperplasia of subperiosteal bone.[1] The onset of the condition is from birth to 6 months of age[2] and is associated with varying systemic symptoms. Fever and hyperirritability are the most common symptoms, but tenderness, dysphagia, pseudoparalysis, pleurisy, and pallor also occur.[1] The etiology of the condition has not been definitely proved, although one study would indicate that it is an exaggeration of a normal process found in many healthy infants.[3] The condition is for the most part self-limited and usually no permanent deformity results, although such is possible in the more severe cases. Laboratory studies are of value only in a negative manner except for the sedimentation rate which is frequently elevated during the acute stages of the disease.[4]

One wonders from the clinical course, herein observed, whether or not a significant number of patients diagnosed as having "colic," milk allergy, and related conditions might not actually represent cases of infantile cortical hyperostosis. Unless this condition is considered and appropriate x-ray examinations conducted, it would be relatively simple to miss the diagnosis if the bone lesions were not large enough to attract the examiner's attention.

SUMMARY

An unusual case of infantile cortical hyperostosis is presented. It is theorized, from the clinical picture described, that a significant number of illnesses described as colic, milk allergy, and related conditions may be symptoms of cortical hyperostosis. If this condition is kept in mind and appropriate x-ray examination conducted, an increasing number of these cases may be accurately diagnosed.

REFERENCES

1. Chapple, C. C.: Nelson's Textbook of Pediatrics, Philadelphia, 1954, W. B. Saunders Co., p. 1343.
2. Caffey, J.: Brennemann's Practice of Pediatrics, vol. 4, Hagerstown, 1954, W. F. Prior Co., Inc., chap. 23, p. 71.
3. Ditkowsky, S. P., and Goldman, A.: Personal communication.
4. Caffey, J.: Brennemann's Practice of Pediatrics, Hagerstown, 1954, W. F. Prior Co., Inc., p. 82.

Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THIS was the first Children's Medical Center admission of a 2-hour-old white male, referred with the diagnosis of erythroblastosis fetalis due to Rh incompatibility.

He was the product of the third pregnancy of an Rh-negative mother whose anti-Rh titer was 1:8 in albumin, four weeks prior to delivery. The mother's first pregnancy resulted in a spontaneous abortion; her second, in an 8 pound 11 ounce infant by cesarean section because of cephalopelvic disproportion. The latter child never had any evidence of hemolytic disease. The present pregnancy was uneventful and was terminated at thirty-eight weeks' gestation by elective repeat section. The birth weight was 7 pounds 12 ounces and the baby "appeared poor," so was referred to The Children's Medical Center. A review of the family history revealed neither anemia nor jaundice.

On admission the physical examination revealed a pale, icteric, edematous, tachypneic, and obviously ill child. The temperature was 98.6° F. by rectum, the pulse 146 per minute, and the respirations 60 per minute. Periorbital edema and scleral icterus were noted. The lungs were clear and the heart was not enlarged. The liver was enlarged to 6 cm. below the costal margin, and the spleen 3 cm. The general activity and tone were poor, as was the Moro reflex.

The laboratory findings on admission included a blood hemoglobin of 7.2 grams per cent. The blood type was O, Rh positive, and the Coombs test gave a four-plus reaction. The mother's blood was typed as A, Rh negative.

Immediately on completion of the laboratory tests, the infant was given an exchange transfusion with fresh Group O, Rh-negative blood. At the time of transfusion, 565 c.c. of blood was removed and 525 c.c. replaced. The hemoglobin level immediately before the exchange was 5.0 grams per cent, and the serum bilirubin 0.7 mg. per cent direct, and 15.5 mg. per cent total. After the exchange, the hemoglobin level was 10 grams per cent, the bilirubin 1.3 mg. per cent direct, and 8.5 mg. per cent total.

The infant seemed somewhat improved and was placed in an Isolette with Mistogen, in the newborn nursery, and started on intramuscular oxytetracycline and vitamin K. Over

the next fifteen hours his bilirubin climbed again to 0.8 mg. direct and 23.0 mg. total, with hemoglobin 9.9 grams per cent. A second exchange transfusion with fresh Group O, Rh-negative blood was done with 545 c.c. removed and 505 c.c. replaced. The venous pressure was 90 mm. H_2O on completion. After exchange, his respiratory rate and pulse rose to 120 and 180, respectively. Hemoglobin had dropped twelve hours later to 6.2 grams per cent. He was then given 35 c.c. packed red cells intravenously and digitalized with digitoxin. Subsequent to this he improved over the next forty-eight hours, so that by age 4 days he seemed in good condition. Serial bilirubins showed another rise after the second exchange to a maximum of 5.7 mg. per cent direct and 19 mg. per cent total at age 14 days, and then there was a rapid drop.

Intervening laboratory studies meanwhile showed a normal urinalysis except for single plus Benedict's test and peripheral leukocyte count of 30,000 per cubic millimeter with 15 per cent lymphocytes, 80 per cent polymorphonuclear cells, 3 per cent monocytes, and 50 nucleated red cells per 100 white blood cells. An electrocardiogram showed normal right ventricular hypertrophy and a digitalis effect.

Suddenly, on the sixth day of life, the baby began to vomit blood-flecked material and pass blood-tinged stools. A platelet count was 39,000 per cubic millimeter and the hemoglobin was 9.4 grams per cent. Both the stools and the vomitus were guaiac four plus. A urine showed 6 to 8 red blood cells per high-power field, and nonprotein nitrogen was 69 mg. per cent. A culture of the blood showed no growth. Nasopharyngeal cultures grew *Colobactrum coli*. Stool culture showed only gamma streptococci.

The infant stopped feeding, and a soft polyvinyl nasogastric tube was inserted. Petechiae appeared on the abdominal wall. A lumbar puncture disclosed xanthochromic cerebrospinal fluid with 180 mg. per cent of protein and 90 erythrocytes per cubic millimeter. Gastrointestinal bleeding persisted and the platelet count fell to 7,000 per cubic millimeter. A bone marrow aspiration was done, showing decreased erythroid forms, and megakaryocytes. He was given a platelet transfusion and started on cortisone, chloramphenicol, penicillin, and Gantrisin. The hemoglobin fell to 6.6 grams per cent and he was transfused with fresh blood and packed red blood cells. His abdomen became distended and peristaltic sounds were absent. He was given nothing by mouth, but supplied with intravenous fluids. Ileus was thought to be due to hypokalemia. With potassium supplementation the bowel sounds later returned. Erythromycin was added to his regimen. His condition rapidly deteriorated, with hypothermia 95.2° F., hematemesis, and onset of gasping respirations. He then began to have apneic spells, from the last of which he failed to recover, dying at age 17 days.

DISCUSSION

DR. ISRAEL DAVIDSOHN.*—The infant was admitted to this hospital at the age of 2 hours with a diagnosis of fetal erythroblastosis due to Rh incompatibility. Now that seems to settle the problem, but does it? The fact

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that the mother had an Rh antibody titer, 1:8 in albumin, four weeks prior to delivery means a moderate degree of sensitization, as determined with this technique. The height of the titer depends on the technique used. With enzyme-treated cells, titers are, as a rule, considerably higher than those obtained with some of the other techniques. The first pregnancy resulted in a spontaneous abortion, and the second was terminated by cesarean section. Both of these events, namely, the spontaneous abortion and the cesarean section, are known to favor sensitization of Rh-negative women pregnant with Rh-positive infants. This is important in view of the fact that on physical examination the baby was edematous, and suggests that the true weight was less than 7 pounds 12 ounces. One would expect the third baby to have a birth weight slightly higher than the second baby. In this case, the second baby weighed 8 pounds 11 ounces. We have learned from Dr. Diamond not to give more blood in the course of replacement transfusions than is removed. We find in the record that the pretransfusion hemoglobin was 5 grams, while two hours previously it had been 7.2 grams. In two hours, the baby lost 2 grams of hemoglobin, which indicates that the hemolytic process was progressing rapidly. The infant had a high indirect bilirubin of about 15 mg. per cent. This is the most important fraction of bilirubin from the point of view of possible damage to the central nervous system. Fifteen hours after the exchange transfusion, the bilirubin rose to 23 mg. per cent, almost all indirect bilirubin, but the hemoglobin remained approximately at the immediate posttransfusion level. A second exchange transfusion was done with fresh O, Rh-negative blood. At this exchange, again, more blood was removed than given. After the transfusion, the respiratory rate and pulse rose to 120 and 180, respectively, which may indicate respiratory and cardiac embarrassment. The hemoglobin continued to drop after the second transfusion. It would be interesting to know at this point whether the Coombs test remained positive after the transfusions, or whether it first became negative, as is the case frequently, and then turned positive again. If this whole illness is due to erythroblastosis secondary to Rh incompatibility, one would expect a persistently positive Coombs test accompanying the progressive hemolysis.

Suddenly, on the sixth day of life, the baby began to vomit blood and passed blood-tinged stools. He had a thrombocytopenia of 39,000 per cubic millimeter, but the hemoglobin remained about the same. The serum nonprotein nitrogen was elevated to 69 mg. per cent, which may be due to involvement of the kidney but may also be due to blood being present in the gastrointestinal tract.

What makes the case especially interesting is the thrombocytopenic purpura which complicates the established hemolytic disease of the newborn infant. Thrombocytopenic purpura may occur as a complication of fetal erythroblastosis, but in usual cases, especially when fresh blood is given, the response is different. Thrombocytopenia in the newborn child may be caused by an immune reaction. The immune thrombocytopenic purpura in the newborn baby is due to an antibody or antibody-like substance which is transmitted from the mother to the

baby through the placenta. There are two varieties of immune thrombocytopenia in the newborn infant; in the first, the so-called auto-immune thrombocytopenic purpura, the mother develops an antibody against her own platelets. This mechanism is similar to the one operative in auto-immune hemolytic disease which is found in some cases of acquired hemolytic anemia. In those cases, the mother has not only thrombocytopenia; she has also the so-called "thrombocytopenic factor" in her blood, which can be demonstrated in two ways: (1) a transfusion of the mother's blood or plasma into a normal person brings on a temporary thrombocytopenia; (2) transfused labeled platelets do not survive the expected normal number of days. There are cases in which the mother has the thrombocytopenic factor but no thrombocytopenia.

The second variety is the so-called "iso-immune thrombocytopenia." The mother develops, during pregnancy, antibodies against an antigenically heterologous group factor in the platelets of the infant. The factor is transmitted from the fetus to the mother and the antibodies from the mother to the baby, through the placenta, in the same way that the Rh antibodies are transmitted. In such cases, the mother does not have thrombocytopenia. Could it be so in this case? The baby was Group O and the mother, A. Blood group factors have been found in platelets, and although there is no complete agreement between the blood factors and the platelet factors, one can assume that such a thing can happen, because persons in blood group A, especially those who belong to subgroup A_1, may have agglutinins known as Alpha-2 which react with red cells of Group O. This occurrence, then, is theoretically possible. However, I will assume that this does not hold in this case because I am sure that those who have attended the child must have thought of it. I would rather consider that the decrease of platelets is a symptomatic thrombocytopenia on an infectious basis.

All kinds of infections—in this case possibly *C. coli*—may bring on thrombocytopenia. A still more tempting diagnosis is that we may be dealing with generalized cytomegalic inclusion disease. The clinical picture of this disease is characterized by prematurity, by jaundice, anemia, and thrombocytopenia. The fundamental work on this condition was done by Dr. Farber and the late Dr. S. Burt Wolbach.[1] They showed that inclusions are found in from 10 to 32 per cent of newborn infants. Inclusions do not necessarily lead to disease, except in a small fraction of cases. We must assume that some other factor is needed to make the disease manifest in babies who are simply carriers of the virus (if it is a virus). It may not be an accident that a number of these cases have been reported in association with fetal erythroblastosis. One of our own cases was in an erythroblastotic infant. It may be that fetal erythroblastosis creates a *locus minoris resistentiae*.

In conclusion, in my opinion, fetal erythroblastosis was not the cause of death in this case. This baby died from thrombocytopenic purpura and its complications. The thrombocytopenic purpura may have been idiopathic, but it is more likely to be on the basis of a viral infection, possibly cytomegalic inclusion disease, or a complication of a bacterial infection.

Fetal erythroblastosis may have been present—it probably was present. Death was caused by the hemorrhagic tendency. Kernicterus may have been found at post mortem, in spite of the fact that the infant's jaundice has decreased. Kernicterus has been found in association with generalized cytomegalic inclusion disease without accompanying erythroblastosis.

Dr. Louis K. Diamond.—I would like to point out, and this is a matter of local pride, that when we say a baby has erythroblastosis based on Rh incompatibility, that diagnosis is usually pretty well established, as in this case; but rarely, we hope, does the patient die of that disease. As Dr. Davidsohn intimated, erythroblastosis, if the diagnosis is established early and if the baby is viable, is in moderately good shape, and is treated promptly, is a disease from which the infant recovers. This has been true in better than 95 per cent of all the cases we have seen in the last five years. This means that if the baby fails to do what he should do after adequate treatment, one should accept only with difficulty the concept that the baby represents an atypical case of a typical disease. One gets into trouble trying to assign bizarre findings to atypical states, rather than looking for another diagnosis. Here is one case where it should be permissible, and in fact is necessary, to make two diagnoses, rather than to hold to one. The persistence of the thrombocytopenia beyond the third or fourth day in a baby with erythroblastosis is most unusual and must be considered as evidence of some other process. On the basis of statistics, one would be justified in considering pyogenic infection as a possible complication of this child's erythroblastosis. Infection in this age group will cause thrombocytopenia, depress and destroy the bone marrow more rapidly and more commonly than any other single complication. The relative erythroid hypoplasia of the hematopoietic system, which we have seen many times in babies with erythroblastosis, is a fairly mild condition. After exchange transfusion or no treatment at all, the bone marrow, from the first week to the third week, shows relatively few erythroid elements but does show normal myeloid forms and normal megakaryocytes. In this baby, the bone marrow aspiration did not show this, even with normal megakaryocytes and a normal distribution of white cells, which suggested that some other process than erythroblastosis was present. We agree with Dr. Davidsohn that occasionally the auto-immune mechanism, meaning platelet antibodies in the mother, will cause thrombopenic purpura in the child. We have not found that with any frequency in erythroblastosis, although it has been so assumed by some investigators. I think possibly the urinary finding of erythrocytes simply indicated local symptomatic bleeding in the urinary tract from the thrombocytopenia. One further point I would like to make is that in our clinic, where bilirubins are followed quite meticulously for the first week of life and where the bilirubin level is kept below 20 to 25 mg. per cent if necessary by exchange transfusion, we have not in the last five years seen kernicterus develop. In this infant, except for two occasions right after birth and just before the second exchange transfusion when the levels were high, all

the other indirect bilirubin levels were well below 15 mg. per cent, and finally, I think, somewhere below 5 at the time of death. Therefore, I should doubt that possibility in this baby.

DR. CRAIG.—Dr. Davidsohn, two days before death the direct serum bilirubin was 2.1 mg. per cent and the total 3.6 mg. per cent, and on the day of death the direct serum bilirubin was 0.95 mg. per cent and the total 1.9 mg. per cent. Do these levels help you at all in excluding or including cytomegalic inclusion disease?

DR. DAVIDSOHN.—I do not think that would be helpful in view of the other studies on bilirubin and it is not likely that there will be kernicterus, but I have seen cases where there was an elevation of indirect bilirubin of over 20 mg. per cent for just a few hours and the patient died subsequently with kernicterus. That is why I said I would not be surprised to find kernicterus here.

DR. CRAIG.—Would the presence of a very low hemoglobin and direct bilirubin on the first specimen influence your consideration of the presence of cytomegalic inclusion disease?

DR. DAVIDSOHN.—I have considered the possibility of both fetal erythroblastosis and cytomegalic inclusion disease being present.

DR. SYDNEY GELLIS.—I would like to ask Dr. Davidsohn what role the transfusion itself might have played in producing the depressed platelet count. Could it be a "washing-out" phenomenon of the platelets by the exchange transfusions?

DR. DAVIDSOHN.—I considered that. You are familiar with the report of Stefanini and Chatterjea[2] on adults, that in replacement transfusions, one might get a thrombocytopenic purpura; but here fresh blood was given on both occasions, with a normal platelet count. For that reason I would say that this was not as likely as in an adult where we do not use fresh blood. It is possible that there is some damage due to the replacement transfusion alone, but I would not consider it too significant in this case.

DR. CRAIG.—How long did the thrombocytopenias discussed by Stefanini and Chatterjea last?

DR. DAVIDSOHN.—I do not remember. I think they make a point of the fact that they were easily corrected. Here, in spite of all these efforts, the condition was not corrected.

DR. GELLIS.—I think there was a report[3] in the *J. A. M. A.* two weeks ago; two erythroblastotic infants developed thrombocytopenia, but I do not think it persisted the way this did.

Was the urine examined for inclusion bodies?

DR. SAMUEL KATZ.—No, it was not.

DR. FARBER.—Dr. Katz, what was the house diagnosis on discharge?

DR. KATZ.—The house diagnoses were: erythroblastosis fetalis, due to Rh incompatibility, congenital hypoplastic anemia, and probable septicemia with bronchopneumonia.

DR. CRAIG.—I think perhaps the protocol did not bring out quite how much icterus this child still had (at least as we saw it), and I suspect, perhaps, it may be due to the fact that he lost bile pigment from the skin and liver more slowly than he did in the serum, because he was very markedly

Fig. 1.

Fig. 2.

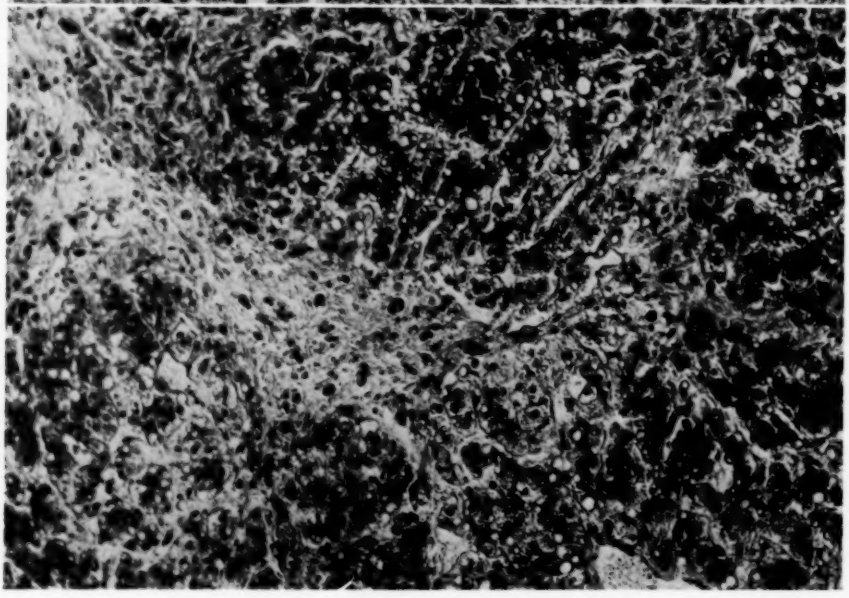

Fig. 1.—Lung. There is diffuse hemorrhage in the alveolar spaces and bronchioles, with atelectasis and edema. (Hematoxylin and eosin; ×110.)

Fig. 2.—Liver. The widened portal triads are devoid of hematopoietic elements. A few bile plugs are present in the bile canaliculi at the periphery of the slightly distorted liver cell cords. (Hematoxylin and eosin; ×150.)

icteric at autopsy. In addition to the child's icterus, he had numerous petechiae of the skin and stomach and massive bleeding into the lungs (Fig. 1) and gastrointestinal tract, changed blood filling the entire small intestine. The myocardial cells histologically contained much glycogen, though there was no associated hypertrophy of the heart.

plasia being chiefly noticeable in the myeloid elements, with a relative decrease in the erythroid elements. The megakaryocytes were strikingly decreased in number throughout the marrow, many high-power fields containing none at all (Fig. 3). There was no evidence of sepsis, either histologically or bacteriologically, cultures being negative both before and

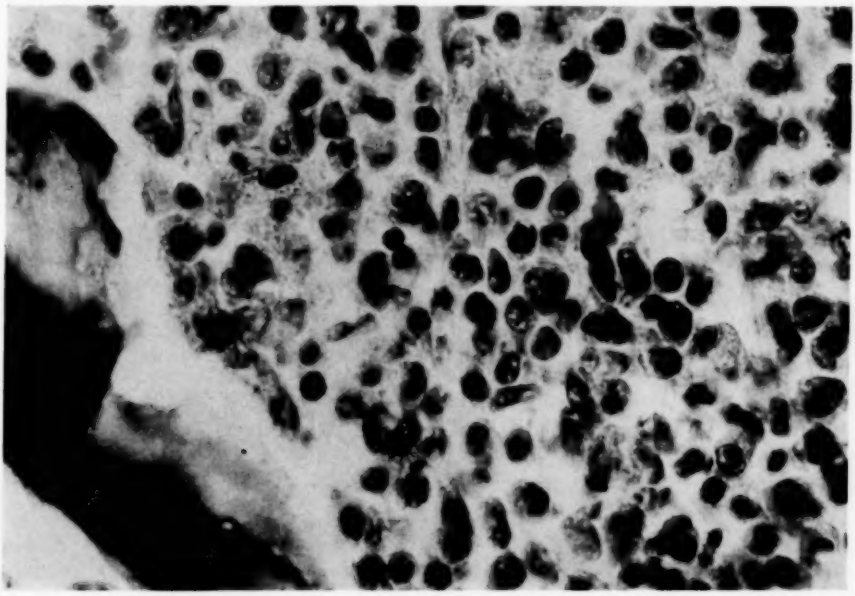

Fig. 3.—Bone marrow. The marrow has an increased cellularity, chiefly of myeloid forms. No megakaryocytes are present. (Hematoxylin and eosin; ×600.)

The spleen was about 40 per cent overweight for the age and there was minimal evidence of continuing extramedullary erythropoiesis. No histological evidence of hypersplenism was present. The liver was greatly enlarged and green, due to bile stasis in liver cells, Kupffer cells, and bile canaliculi. There was no evidence of hepatitis or of generalized cytomegalic inclusion disease (Fig. 2). The bone marrow was hyperplastic, the hyper-

after death. The case then is regarded as one of fetal erythroblastosis with clearing jaundice and thrombocytopenia leading to death with massive hemorrhage. The thrombocytopenia was secondary to the failure of the megakaryocytic elements, the etiology of the latter not being known. Dr. Diamond, if one of the immune mechanisms mentioned above was indeed active, would you expect a decrease in the number of megakaryocytes as well as platelets?

DR. DIAMOND.—I would, yes. I have no idea why this child's megakaryocytes and platelets were so decreased. If it had been just a result of the exchange transfusions we would have expected that our attempt to improve his platelets by giving him fresh platelet transfusions should have corrected it, as it has corrected other children's.

DR. FARBER.—I would like to ask Dr. Diamond and Dr. Davidsohn whether we could not clarify the nomenclature a great deal by dropping the term, "erythroblastosis fetalis." It has served its purpose when used as a descriptive term. I think we have been able to show for many years that there are a number of different diseases which will produce this clinical picture, the most common of which is that due to Rh incompatibility. I think Dr. Davidsohn has brought out very clearly that cytomegalic inclusion body disease is one of the number of conditions which may produce a clinical picture of erythroblastosis fetalis. Of the three diagnoses which were mentioned, we may assume that one, the Rh incompatibility, was proved by Dr. Diamond's studies. We have no anatomical proof of that, but the findings are consistent with it. The second diagnosis, of the thrombocytopenic purpura, which Dr. Davidsohn made, and with which Dr. Craig is in agreement, was the actual cause of death. So far as the third is concerned, Dr. Davidsohn, if Dr. Craig is as much of a gentleman as I know he is, he will restain those slides and find the inclusion bodies.

REFERENCES

1. Farber, S., and Wolbach, S. B.: Intranuclear and Cytoplasmic Inclusions, Am. J. Path. **8**: 123, 1932.
2. Stefanini, M., and Chatterjea, J. B.: Studies on Platelets. IV. A Thrombocytopenic Factor in Normal Human Plasma, Blood, and Serum, Proc. Soc. Exper. Biol. & Med. **79**: 623, 1952.
3. Krevans, J. R., and Jackson, D. P.: Hemorrhagic Disorder Following Massive Whole Blood Transfusions, J. A. M. A. **159**: 171, 1955.

Medical Progress

POISONOUS PLANTS

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THE ingestion of poisonous plants by children is not an important cause of serious trouble numerically as compared to household poisons such as disinfectants and other common medicaments, especially lye, kerosene, barbiturates, and salicylates.[1, 2] Yet when a child has tasted or eaten a suspicious plant, it is important to be able to recognize the plant and to know what part of it, if any, is poisonous: root, stem, leaves, blossoms, or fruit.

The purpose of this paper is to list the plants which are capable of producing toxicity and to describe the more important in the simplest terms so that an untrained person may identify them with some degree of assurance. Since ready references for physicians are lacking, I thought it well to provide this information. Most of the available data are designed for use by those interested in animal husbandry, for grazing animals suffer mostly from this source of poisoning. For more detail, see *Poisonous Plants of the United States* by Muenscher.[3]

Much folklore surrounds this subject. Some plants, for example, the Indian or snake strawberry (*Duchesnea indica*), are supposed to contain poison, when actually they are harmless. The common pokeweed (*Phytolacca americana*) has a poison in its root, but the young shoots, if boiled in two waters, are edible. Leaves of rhubarb (*Rheum rhaponticum*) have oxalic acid and should be avoided. The Irish potato, a member of the nightshade family, produces an alkaloid solanine in the green shoots or "eyes" of the tubers.

Of the plants which are likely to attract children, only a few contain deadly poisons. These are mushrooms, members of the nightshade family, poison hemlock, and water hemlock. The physician should be able to recognize these plants. He should remember that the noxious chemicals in plants are alkaloids, glucosides, resins, phenols, alcohols, oxalates, and phytotoxins.

Contact dermatitis from irritating plants causes the greatest amount of suffering. The chief offenders are poison ivy and poison oak which are so similar as to be considered the same plant under the Latin name, *Rhus toxicodendron*. Poison sumac (*Rhus vernix*), lady's-slipper (*Cypripedium hirsutum*), and primrose (*Primula*) are irritating to many individuals. The rarer causes of contact dermatitis are too numerous to mention. Also allergens such as ragweed will be

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omitted from this discussion as causes of plant poisoning.

The farmer should be familiar with plants having poisonous seed, which contaminate grain or flour made from grain. They are corn cockle, mustards, flax, lupines, and Jimson weed. The dairyman endeavors to prevent his cattle from grazing on certain plants—wild onions, garlic, yarrow, buttercup, dock, tansy, ragweed, mustards, and chicory—which give an unpleasant flavor to milk. The only dangerous plants in this group are white snakeroot (*Eupatorium rugosum*) and rayless goldenrod (*Aplopappus heterophyllus*). They produce an alcohol, tremetol, which causes muscular weakness in cattle and in human beings who drink milk thus contaminated. Nancy Hanks is the most famous victim.[4] White snakeroot is a perennial herb which grows 3 to 10 feet high. The stem is simple, in some cases branching above, slender, and smooth. The leaves are 2 to 4 inches in length, oval, and pointed at the tip. They have serrated edges. The flowers are tiny white disks 5 to 7 mm. in diameter. Many flowers are grouped in a dense flat cluster at the end of stems, and resemble the garden ageratum. Its distribution ranges from eastern North America westward to Minnesota and Texas, in woodlands, damp or shaded pastures, and fields. The rayless goldenrod is a perennial herb which grows 1 to 4 feet high. The stem is stout, erect, and simple or sparingly branched. The leaves are alternate, linear, entire, or toothed. The flowers are composed of 7 to 15 small, yellow tubules clustered in heads at the tops of stems. The rayless goldenrod is found only in the southwestern part of the United States.

Several ornamental garden plants contain known toxins and will be mentioned briefly because they are relatively unimportant. Lily of the valley (*Convallaria majalis*), oleander (*Nerium oleander*), and foxglove (*Digitalis purpurea*) have cardiac glucosides in their leaves. The opium poppy (*Papaver somniferum*), a common garden flower, contains the source of opium in the juice of its capsule. The very fragrant vine of southeastern United States, yellow jessamine (*Gelsemium sempervirens*), has a poison in all its parts. Narcissus bulb, daphne berries, privet berries (*Ligustrum vulgare*), larkspur seed (*Delphinium*), castor bean (*Ricinus communis*), and Jerusalem cherry (*Solanum pseudocapsicum*), all are toxic if eaten by children.

Several familiar trees produce poisons: the nut of the buckeye or horse chestnut tree (*Aesculus*), the bean of the Kentucky coffee tree (*Gymnocladus dioica*),[5] the inner bark of black locust (*Robinia pseudoacacia*) (which children have been known to chew), the leaves of box bushes (*Buxus sempervirens*), and all parts of the yew tree (*Taxus*) are poisonous.

The men of Lewis and Clark's expedition used flour made of the bulb of the camas lily (*Zygadenus*) of the western plains and suffered violent intestinal symptoms.[6] The Nez Percé Indians, however, relished this food and later battled the white man who settled on their camas fields. Two alkaloids in the death camas are zygadenine and veratrine. The latter chemical is also found in *Veratrum viride* or false hellebore, another member of the lily family. But the false hellebore has a burning taste which protects

all but the hungriest of animals and the most curious of children. Others have mistaken the roots of monkshood (*Aconitum*) for horseradish and the shoots of mountain laurel (*Kalmia latifolia*) for wintergreen.[7] Honey made from laurel or other members of the heath family is poisonous.[8] Just as the Nez Percé Indian was able to profit by the bulb of the camas but not the white man, so, too, can deer browse on mountain laurel with gusto while cattle, goats, sheep, and man are made ill by it. Thus we see natural adaptability exhibited by the Indian and deer.

Poison ivy (*Rhus toxicodendron*) is a common and widespread woody shrub or vine (Fig. 1, *F*). Its leaves are alternate, compound with three

Fig. 1.—*A*, Deadly amanita (*Amanita phaloides*). *B*, The fly mushroom (*Amanita muscaria*). *C*, Lady's-slipper (*Cypripedium hirsutum*). *D*, Jimson weed (*Datura stramonium*). *E*, Poison sumac (*Rhus vernix*). *F*, Poison ivy (*Rhus toxicodendron*). *G*, Black nightshade (*Solanum nigrum*). *H*, Water hemlock (*Cicuta maculata*). *I*, Poison hemlock (*Conium maculatum*). (Copyright, 1939, by General Biological Supply House, Inc., Chicago, Ill.)

leaflets, and usually shiny. The flowers consist of small, yellow-green petals. They are followed by small, white- or cream-colored berries. All parts of this plant contain urushiol, a yellowish slightly volatile oil or resin, which is very irritating to the skin of most human beings. A similar poison is found in all parts of the large shrub or small tree occurring mostly in swamp and bog. It is called poison sumac (*Rhus vernix*) (Fig. 1, *E*). The flowers and fruit are similar to those of poison ivy but the leaves resemble those of other sumac plants.

Another type of irritant, probably a fatty acid, in the glandular hairs of stems and leaves of the lady's-slipper (*Cypripedium hirsutum*) (Fig. 1, *C*), produces a vesicular dermatitis in susceptible individuals. This orchid is a woodland flower of spring. A fourth common cause of contact dermatitis is the primrose (*Primula*). It has been estimated that 6 per cent of individuals are susceptible to an irritating phenol called primin, secreted by its hairy stem and leaves. There are several varieties of this little early summer garden plant usually 4 to 6 inches high. At the top of a single stem one sees a cluster (or umbel) of funnel-form yellow, pink, or lilac flowers. From the base of the stem radiate six to eight fuzzy green leaves with wavy margins.

The family of plants known as the nightshade includes such familiar members as the Irish potato, tomato, tobacco, belladonna (deadly nightshade), and an ornamental potted plant, Jerusalem cherry. Among the uncultivated members of this family the Jimson weed (*Datura stramonium*) is perhaps the most toxic, as it contains the alkaloid hyoscyamine. Children have been known to eat the seed.[9]

Jimson weed (Fig. 1, *D*) is a coarse, foul-smelling, annual herb 4 to 6 feet tall with a smooth, green or purple stem which divides and subdivides into many branches. The leaves are alternate simple, ovate, unevenly toothed and have a pungent unpleasant odor. Flowers are white or purplish funnels 4 to 6 inches long, growing in the axils (an angle made by a branch) of the branches. The fruit which follows the flower is a prickly pod or capsule divided into four cells. Each compartment produces many small dark seeds. The Jimson weed is found in waste places widespread across the United States. A cousin, black henbane (*Hyoscyamus niger*), is found in the northern states and Canada, especially in the Northwest.

Other members of the family which are poisonous contain the toxic alkaloid solanine in the fruit. The black nightshade (*Solanum nigrum*) (Fig. 1, *G*) is an annual herb, 1 or 2 feet high, which grows in fields and waste places across the United States. The blossoms are small, white, star-shaped flowers, followed by purple or black berries. The leaves are smooth and have wavy margins. The blue nightshade (*Solanum dulcamara*) differs from the above by having blue or purple wheel-shaped flowers and red berries. The wild tomato (*Solanum carolinense*) is a perennial herb with spiny stem and leaves. Its flowers are lavender or white, and its berries are yellow.

Two mushrooms (Fig. 1, *A* and *B*) and two members of the parsley family vie for first place among the more deadly poisonous members of the plant kingdom. Though most mushrooms

TABLE I

COMMON NAMES	LATIN NAME GENUS AND SPECIES OR SURNAME AND GIVEN NAME	TYPE OF CHEMICAL	PART OF PLANT
1. Pokeweed Scoke	*Phytolacca americana*	A saponin or glucoside	Root
2. Rhubarb Pie plant	*Rheum rhaponticum*	Oxalic acid	Leaves
3. Poison ivy Poison oak Poison creeper Three-leaved ivy Piery Mercury	*Rhus toxicodendron*	Resin urushiol	All parts
4. Poison sumac Poison dogwood Poison elder Poison ash Swamp sumac Thunderwood	*Rhus vernix*	Resin urushiol	All parts
5. Lady's-slipper	*Cypripedium hirsutum*	Fatty acids	Hairs of stem and leaves
6. Primrose	*Primula obconica* *Primula malacoides* *Primula auricula* and other species	Phenol primin	Hairs of stem and leaves
7. White snakeroot Richweed White sanicle	*Eupatorium rugosum* *or urticaefolium*	Alcohol trematol	Leaves and stems
8. Rayless goldenrod	*Aplopappus heterophyllus*	Alcohol trematol	Leaves and stems
9. Lily of the valley	*Convallaria majalis*	Glucosides convallarin and convallamarin	Leaves and flowers
10. Oleander	*Nerium oleander*	Glucosides nerioside and oleandrosides	Leaves
11. Foxglove	*Digitalis purpurea*	Glucosides digitoxin digitalin digitonin	Leaves
12. Opium poppy	*Papaver somniferum*	Alkaloids of opium	Juice of unripe capsule
13. Yellow jessamine False jessamine	*Gelsemium sempervirens*	Alkaloids gelsemine and gelseminine	All parts
14. Narcissus	*Narcissus poeticus*	Alkaloids?	Bulbs
15. Daphne	*Daphne mezereum* *Daphne cneorum*	Glucoside daphnin	Berries
16. Privet	*Ligustrum vulgare*	Not known	Berries
17. Larkspur	*Delphinium*, several species	Alkaloid delphinine	Seed
18. Castor bean Palma Christi	*Ricinus communis*	A phytotoxin ricin	Seed

(Continued on next page.)

TABLE I—CONT'D

COMMON NAMES	LATIN NAME GENUS AND SPECIES OR SURNAME AND GIVEN NAME	TYPE OF CHEMICAL	PART OF PLANT
19. Jerusalem cherry	*Solanum pseudo-capsicum*	Alkaloid solanine	Fruit
20. Buckeye Horse chestnut	*Aesculus*, several species	Glucoside aesculin	Seed
21. Kentucky coffee tree	*Gymnocladus dioica*	Alkaloid cytisin	Seed
22. Black locust	*Robinia pseudoacacia*	Phytotoxin robin	Inner bark
23. Box	*Buxus sempervirens*	Alkaloid buxine	Leaves and twigs
24. Yew	*Taxus*, several species	Alkaloid taxine	All parts
25. Death camas	*Zygadenus*, several species	Alkaloids zygadenine veratrine and others	Bulb or root
26. False hellebore	*Veratrum viride*	Alkaloids veradridine veratrine and others	All parts
27. Monkshood	*Aconitum*, several species	Alkaloids aconitine aconine	Roots and seeds
28. Mountain laurel	*Kalmia latifolia*	Resin andromedotoxin	Leaves and twigs
29. Jimson weed Jamestown weed Thorn apple	*Datura stramonium*	Alkaloid hyoscyamine	Seeds and leaves
30. Black henbane	*Hyoscyamus niger*	Alkaloid hyoscyamine	All parts
31. Black nightshade Poison berry	*Solanum nigrum*	Alkaloid solanine	Green fruit
32. Blue nightshade European bitter-sweet Woody nightshade	*Solanum dulcamara*	Alkaloid solanine	Green fruit
33. Wild tomato Horse nettle Bull nettle Sand briar	*Solanum carolinense*	Alkaloid solanine	Green fruit
34. Water hemlock Cowbane Beaver poison	*Cicuta maculata*	Resin cicutoxin	Roots
35. Poison hemlock Deadly hemlock Poison parsley	*Conium maculatum*	Alkaloid coniine	All parts

are edible, all wild varieties should be considered dangerous, for the differentiation between the good and harmful varieties is too difficult for anyone but a trained mycologist.

The botanical name of the parsley family is Umbelliferae. It is so named because the many tiny flowers are clustered together in an umbrella-like clump at the top of a stem or branch, like those of Queen Anne's lace (*Daucus carota*), which grows everywhere and is therefore the most familiar member. It is mentioned here merely to introduce the family, for it is not poisonous. The two deadly members are water hemlock (*Cicuta maculata*) (Fig. 1, *H*) and poison hemlock (*Conium maculatum*) (Fig. 1, *I*). These two plants are taller than Queen Anne's lace, usually 3 to 6 feet, and have smooth greenish stems dotted with purplish macules or blotches. The stems branch freely. The former contains the resin, cicutoxin, in the root which produces convulsions; and the latter contains the alkaloid coniine in all parts, and this paralyzes the muscles of respiration.

The Greeks in the time of Socrates executed political prisoners by means of this poison. More recently people have been poisoned by mistaking the seed for anise, the leaves for parsley, and the roots for parsnips and artichokes.

Treatment of plant poisoning is the same as that for other forms of acute intoxication plus the use of any known physiologic or pharmacologic antidote.

Table I gives a list of poisonous plants.

SUMMARY

This paper has to do with plants which are likely to make children sick. It attempts to progress from the less to the more poisonous.

Included is a table of plants with their scientific names, and listing the toxic substances contained in the various parts of the plants.

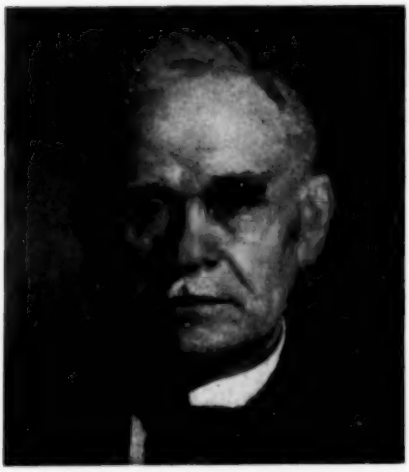
REFERENCES

1. Swinscow, D.: Accidental Poisoning of Young Children, Arch. Dis. Childhood **28**: 26, 1953.
2. Arena, J. M.: The Problem of Accidental Poisoning in Children as It Exists Today, J. A. M. A. **159**: 1537, 1955.
3. Muenscher, W. C.: Poisonous Plants of the United States, New York, 1951, The Macmillan Co.
4. DeVoto, B.: Frontier Family Medicine, What's New **192**: 5, 1955.
5. Massey, A. B., and Hatch, R. D.: Poisonous Plants, Bull. Virginia Polytechnic Inst. **36**: 31, 1943.
6. DeVoto, B.: The Journals of Lewis and Clark, Boston, 1953, Houghton Mifflin Co., pp. 240-241.
7. Aikman, J.: Dangerous Drugs and Poisons, Brennemann and McQuarrie Practice of Pediatrics, W. F. Prior Co., Inc., vol. 1, chap. 17, p. 31, 1948.
8. Pammel, L. H.: A Manual of Poisonous Plants, Cedar Rapids, Iowa, 1911, The Torch Press, p. 64.
9. Mitchell, J. E., and Mitchell, F. N.: Jimson Weed (Datura Stramonium) Poisoning in Childhood, J. PEDIAT. **47**: 227, 1955.

Pediatric Profiles

Isak Jundell

(1867-1945)



From an oil painting by D. Tagtstrom

ON Christmas Eve, 1945, Dr. Isak Jundell, Emeritus Professor of Pediatrics, died at the age of 78. The cause of death was cardiosclerosis. During his last year he had suffered from progressive cardiac failure and had several severe heart attacks. However, he continued his former busy life as Editor of *Acta Paediatrica* and attended scientific sessions.

His last active participation in a scientific discussion was one month before his death. On this occasion he suffered a very severe attack of pulmonary edema, and it was not until he had restored himself somewhat that he was able to return home. He tried as much as possible to hide the symptoms and signs of his disease, as he did not like to be the object of other people's pity. He did not want to cause trouble or inconvenience, and he even walked alone, so that his slow gait, made necessary by his condition, would not be a nuisance for others. In full keeping with his modesty, he had expressed his desire that he should be buried quietly and that his death should not be announced until after the burial. Although his final sickness did not last long, it was very painful for him. However, he was fully aware of his surroundings until the very end.

With the passing of Isak Jundell, one of the most prominent pediatricians that Sweden ever possessed disappeared. He was a pioneer in the art of pediatrics and child health, and a scientist well known in international circles. His whole life was filled with work in the service of mankind: scientific research, pediatric practice, and the social welfare of children. He took an essential part in and made many valuable contributions to the flourishing period of pediatrics during the first decades of this century, when it at last was accepted as a specialty within internal medicine. It was at this time that the modern art of pediatrics was founded.

Isak Jundell's father, a dealer in antiques and owner of a curiosity shop, emigrated to Sweden from Germany around 1860. He first went to the small bishopric of Växiö but soon moved to Stockholm. He had eighteen children, half of whom died in childhood. As a result, Isak was the oldest of the surviving nine brothers and sisters. The family lived under very poor conditions, and during his school days, as well as during his medical studies, Isak had to earn his own livelihood by doing an extra job as a so-called informator, teaching and helping younger school children with their lessons. He studied medicine for nine years at the Royal Caroline Institute in Stockholm where he was graduated in 1895.

Jundell devoted the first part of his postgraduate training to internal medicine as assistant at the University Hospital, Serafimerlasarettet. It was not until five years later that he started his pediatric career. In 1900 he was appointed assistant at the pediatric clinic of Oscar Medin and remained there for two years. His interests in social pediatrics drove him to devote a great part of his time to various kinds of institutions for the welfare of children then existing in Stockholm. He completed his pediatric education by several longer or shorter periods of study abroad at renowned pediatric centers on the Continent, especially in Germany and Austria. In the meantime, in 1907, he was appointed head of a municipal department of internal medicine in Stockholm and remained in that position until he became professor of pediatrics.

In the beginning his principal interest was doubtless neither internal medicine nor pediatrics, but bacteriology. Even in 1892, before graduation, he studied bacteriology in Vienna. In 1899 he served at the Institute for Infectious Diseases in Berlin and in 1900 at the Pasteur Institute in Paris. At that time there was no special bacteriological institution in Sweden and no possibility of earning a living as a bacteriologist. Because internal medicine at that time was the clinical specialty nearest to scientific bacteriology, Jundell decided to be an internist. When he was a resident in internal medicine at the University Clinic, he sometimes worked as a physician at the municipal venerological department in order to come in contact with and to be acquainted with practical bacteriological problems. During 1901 to 1907 he served as head of the newly established municipal bacteriological laboratory of the City Health Department of Stockholm, and from 1905 to 1909 he was head of the smallpox vaccination department of the Public Health Service.

His keen interest in bacteriology is evident from his extensive publications in this field. The first dozen articles that he published were of pure bacteriological content, and he continued to study bacteriology and the infectious diseases for three decades. He made studies on the gonococcus and meningococcus, on *Hemophilus influenzae*, and diphtheria bacillus. He threw light upon problems regarding the serological diagnoses of Salmonella and its mode of transmission. He made investigations of *Spirochaeta pallida* and of the Wassermann reaction, and he took a position in the discussion on human and bovine tuberculosis. Later he published several articles on B.C.G. vaccination and carried out investigations on scarlet fever.

For many years he was interested in cross-infections in hospitals and their prevention. He tried various prophylactic methods and invented a kind of isolation tent that was used for some time, but finally, as it turned out to be impractical, it was replaced by isolation cubicles. The thesis of Jundell, "Clinical Studies on Bronchitis," was essentially a bacteriological study. In internal medicine he made some interesting studies of the influence of sport and physical exercise on the heart and kidneys and of the prognosis of heart lesions produced by physical stress.

Within pediatrics, there are many areas to which Jundell has made valuable contributions. It is only possible to outline his many varying scientific interests within this specialty, and I will mention only a few of the most important works by which Jundell became internationally known. His first contribution was his study of body temperature in children. He was the first to describe the monothermia of young infants. Probably his most important works, however, were the time-consuming, well-documented, and interesting metabolism studies, partly in healthy infants, and partly in infants with acute diarrhea and infantile cholera. He also made thorough studies of mixed diet during the first year of life and its importance in the prevention of rickets, as well as many other studies on rickets during the 1920's. These latter studies have contributed a great deal to our understanding of both the cause of rickets as well as its prevention, and constitute a valuable corollary to studies made simultaneously in other countries. It is from this period that we have our present knowledge of the connection between rickets and vitamin D deficiency. A great part of his scientific production within the field of pediatrics concerns social medicine. I will return later to his contributions in this field.

That the scientific work of Jundell was appreciated and studied abroad is shown by the frequent quotations and the references given to his articles in the international periodic and monographic pediatric literature, and his election as honorary member to many foreign academies and other scientific societies. Probably it was less his scientific studies than two other very important contributions within pediatrics that made his name well known in international pediatric circles: the initiative for the Second International Pediatric Congress in Stockholm 1930, and the editing of *Acta Paediatrica*.

The First International Congress of Pediatrics met in Paris, 1912, and it was then decided that the next one should be held in Brussels. Then World War I changed the plans. When the war was ended, Jundell had the idea to again assemble the pediatricians of the world in a mutual meeting and this time in neutral Sweden. Not until twelve years later did this project come to fruition. Despite severe opposition and resistance from several quarters, remarkably enough including even some of his own countrymen, Jundell put his plan through. With unbelievable energy and tenacity, he worked for the realization of his plans, traveling all over Europe in order to arouse enthusiasm and to dissolve the hate of former enemies by means of personal pressure and persuasion.

At last Jundell succeeded in his self-elected task, and in 1930 the foremost pediatricians of the world at that time

assembled in Stockholm. The organization of the Congress was perfect, the social entertainments were, according to general opinion, excellent, and the scientific interchange was very great. It was solely the result of Jundell's efforts that the Congress was held and that its success was so definite. As a Swede, I must confess that we pediatricians gained much from that Congress. Our country, its scientific institutions, its social welfare work for children, and its pediatric research work were noticed and appreciated, and the personal connections and relations between Swedish and foreign pediatricians that grew up during this Congress have been of great profit to us.

During the first two decades of this century, Swedish and Scandinavian pediatric research was undeveloped, and it scarcely was noticed abroad. This probably was due partly to the lack of a national forum, in which the result of the research work could be published. It was either printed in the Swedish language in our national journals, and thus became inaccessible to international readers, or articles were sent to foreign, especially German, reviews and thus often lost their Swedish origin. This was the reason why pediatricians from the northern European countries accepted the suggestion of Jundell in 1919 to edit a mutual Scandinavian pediatric journal, and in 1921 the first issue of *Acta Paediatrica* appeared. Jundell was the obvious choice for editor and remained as such until his death twenty-five years later. Because Jundell alone was responsible for *Acta Paediatrica* during these years, the credit is solely his that Nordic pediatric science was made known abroad. It is no secret that he often had great difficulties to solve, many times including economic ones, and the editing of *Acta Paediatrica* without doubt caused Jundell great trouble, worry, and concern. Alone, without aid of a secretary, Jundell managed the whole correspondence, scutinized and judged contributions, controlled the quality of the translations, corrected the proofs, and sought support of advertisers and subscribers. During his last years he was busy preparing a general index to the volumes of the journal which had appeared.

If his greatest international pediatric contributions were the Congress of 1930 and the editing of *Acta Paediatrica*, his greatest national achievement was his pioneer reform within the field of social pediatrics. He has related the following account of how he became interested in social pediatrics. As resident at the Pediatric Clinic at the Foundling Hospital, he was very much impressed and disturbed by the high mortality rate of the infants. During the ten-year period between 1891 and 1900, the mortality rate of infants at that hospital was 20.7 per cent, while the general infant mortality rate in Sweden was only 9.4 per cent, and that for illegitimate infants was 16.1 per cent. The establishment of the Foundling Hospital had apparently been without benefit and, despite the great cost of this work, was apparently doing harm. Jundell started to study the causes of this high mortality rate. He searched along various lines and arrived at the conclusion that the high motality resulted from rapid and premature weaning as well as from the bad habits and the ignorance of the foster mothers. The care of lonely mothers

and their young infants apparently had to be made under quite different conditions than those the Foundling Hospital could offer, and preferably in a manner that permitted mother and child to live together at least during the period of breast feeding. Jundell succeeded in making some warmhearted persons interested in his goal of helping indigent mothers by building a Home for Mothers and Infants, where the mothers could live with their infants during the nursing period. This was the first Home for Mothers and Infants that was built in Sweden and was inaugurated in 1903. Jundell accepted the responsibility of the health control at this home and retained this responsibility until 1910.

The experience that Jundell acquired as physician of this home and from his great pediatric practice that he had started in 1903 kept his mind and interest open to the plight of lonely mothers, and alert to those measures that had to be undertaken for their benefit in Stockholm, as well as in other parts of the country. During the first years of this century, when Jundell campaigned for better means to help distressed mothers with young infants, he was told from authoritative quarters that it was not fitting for a young physician to occupy himself with these problems. He would not be discouraged, however, and continued to deliver suggestions and projects of reform that these and other similar problems aroused. In 1906 he submitted to the newly formed Swedish Association for Social Welfare a proposition containing a detailed program for the social welfare of children. This program included almost all the fields of social pediatrics, mothers' homes, infants' homes, well-baby clinics, measures of improvement of the care of foster children, the need of improved popular enlightenment in child health, and suggestions as to how the various points of the program might be realized. These were ideas that at that time were new, and to many persons they probably seemed to be rather peculiar. During the following forty years, however, most of the points suggested and projected by Jundell have been realized. This constitutes a proof of the cleverness of his judgment, his great experience within social pediatrics and child health, and the profundity of his preliminary studies.

Through these works Jundell was recognized early as a physician interested in social medicine, and it was quite natural that his experience and energy were made use of in social pediatrics. In 1916 he was elected a member of a governmental committee, the task of which was to modernize the then existing rather primitive laws for child welfare. No doubt Jundell left his marks on the propositions of this committee delivered in 1921, which were later passed in the parliament.

When it became evident that the Swedish Association for Social Welfare had to form a special section of child health, Jundell was elected head of it. In this role he had a rich opportunity to promote improvement of child health in Sweden. On his initiative, the Section of Child-health set out a long series of measures aiming at an improved popular enlightenment regarding child care. I will mention only two of these: the organization of the so-called "Demonstration Courses" in child care for women, and the publication and editing of small popular

pamphlets. He also contributed actively himself by giving lectures, writing articles in the journal of the Section of Child-health, and by publishing pamphlets. His small booklet on the care and feeding of infants and children was at that time the most popular book on child care. It was published in thirty-six editions and sold 310,000 copies. A somewhat larger popular textbook on child care also achieved a wide distribution, and without doubt it has improved the art of child care by mothers, nurses, and midwives to a great degree. Jundell remained as chairman of the Section of Child-health of the Swedish Association of Social Welfare until 1943.

Jundell's interest in social pediatrics asserted itself even in quarters other than in the Swedish Association of Social Welfare. In trying to succeed in his various projects, he frequently met difficulties because of the lack of qualified help. There were no nurses especially trained to take up social pediatric work. In order to meet this need, Jundell in 1923 started a course to instruct and train pediatric nurses. In this he collaborated with an important branch of the Nordic Association of Housewives. These qualified nurses, who received the name "Jundellare," have played a very important role in preventive pediatric work in Sweden. It was due almost solely to them that it was possible, in 1937, to introduce the governmentally supported nationwide p e d i a t r i c preventive health scheme in our country. The courses for pediatric nurses continued until 1934, when they were replaced by the State School for Pediatric Nurses, whose administration and mode of training are principally built upon experiences gained by the original Nursing School of the Nordic Association of Housewives. The education and practical training of these pediatric nurses was one of Jundell's greatest interests, and he did everything in order that they should be as highly qualified as possible. It pained him severely that because they had a shorter training in general medicine and in adult nursing than ordinary nursing-school pupils, his training-school students could not be accepted by the Public Health Service as equal to ordinary nurses when it was the question of work at the well-baby clinic.

I will not close these comments on Jundell's role in the formation of social pediatric and public health in our country without at least briefly mentioning his projects to solve the problem of mental health of our people, and his great interest in so-called psychopathic children. For many years he was busy with problems of child education and prevention of maladjustment in children, and it was at his suggestion that this item was put on the program of the Fourth International Pediatric Congress in Rome in 1937 as one of the principal subjects for discussion.

As a teacher in pediatrics, Jundell was much appreciated, and a great number of physicians, now practicing in our country, have received not only their knowledge of child health and diseases from him, but also a great interest in the art of pediatrics as well. As a young undergraduate medical student, I remember very well the interest in pediatrics that Jundell evoked by his exellent teaching during one of his earlier periods as a substitute professor. One got the feeling that with

Jundell a new era of teaching in pediatrics was introduced. Pediatrics developed during his time from a rather small subject to one of the more important branches of medicine for the general practitioner.

It has been said that Jundell was at the same time a man of peace and a fighting man. I do not believe it can be postulated that he asked for a fight for its own sake. His character was without doubt such that he wished to live in peace and harmony with his fellow creatures. Like all pioneers for new ideas, he did not always get the understanding he expected but instead, not infrequently, met resistance to the fulfillment of his projects. Resistance only seemed to spur him to increased efforts. With greater practical skill and undauntedness than diplomatic suppleness, he fought his opponents. He delivered sharp blows and so had to accept hard knocks in return. He never lost his temper and never was discouraged, but continued undaunted in his work, with the untiring energy of the true enthusiast. By his burning eagerness, his stubbornness, and his tenacity, he often succeeded in leading his campaign for his idea or for his project to victory.

Jundell was an extraordinarily generous person. Because his own needs were very small, he gradually attained the position of being able to help others, a position that he made full use of. He supported his nearest relatives generously, and probably only his closest friends know what succor he offered to the distressed and persecuted Jewish race during the Hitler period in Germany. However, Jundell was generous not only to his fellow creatures on a personal level, but he also supported various philanthropical enterprises with a warm heart.

It was a rather common event at the meetings of the Section of Child-health of the Swedish Association of Social Welfare that, when a good project seemed about to be turned down due to a difficult economic situation, Jundell informed the members of the board that he had received a sum of money from a friend, or that there was a foundation with money which he had permission to use exactly for this project. Everyone knew that "his friend" usually was Jundell himself, and that the money of the "foundation" in question came out of his own pocket.

It is rather remarkable that Jundell, who was a real pioneer among the physicians and psychologists endeavoring to penetrate the mysteries of children's souls and minds, who understood children so well, who was so well liked by them and who loved children, never married and had children of his own. Apparently, he sublimated his father instincts by working for the benefit of all children. It seemed that he had found sufficient satisfaction and happiness in the personal contact he had with children in his profession as a pediatrician and with the children in his friends' families. He was a reticent person and seldom talked about his own feelings. However, it was apparent that Jundell began to feel his loneliness, and to regret that he had no children when he had retired from his professorship and was no longer chief of the Nortull Hospital.

Jundell was very considerate and kind and was essentially a humanist. He felt most at ease in a small group of intimate friends where his genuine

amiability and silent humor showed to their best advantage, and in his own nice home, that bore witness of great personal taste, he was an excellent host. He had very little need of change and entertainment. He was rather ascetic, but he could appreciate the enjoyment of a good table, and he found satisfaction in such entertainments that made his friends happy. He loved music and often attended the performances of the opera, especially during the period when his boyhood friend, the famous opera singer John Forsell, appeared. During the summer months he found recreation, happiness, and freedom from worries at his small country cottage on the island of Öland in the Baltic Sea. There he had time to read the nonmedical books that he had missed during the teaching season in Stockholm, and he also had the opportunity to discuss various problems with his faculty colleague, the dermatologist, Professor Johan Almqvist, who died only a few days before his old student friend Isak Jundell.

Isak's school studies were financially supported by the Mosaic parish. In addition he had to offer himself as informator, and he served as informator in several families, among whom was a sea captain, Forsell. With the son of this captain, John, who later became a famous opera singer, Isak formed a friendship that lasted all through life.

Isak lived with his family on the south side of the river Norrström that divides Stockholm into two parts. He had to cross the river in order to attend the lectures in the medical school on the north side. One winter day he had the misfortune when walking on the frozen river to fall through a break in the ice. When he had managed at last to save himself, he found that he had lost his expensive German textbook of anatomy, which was floating in the water. Without hesitating Isak threw himself into the water again and saved the book. He arrived at the classroom thoroughly wet and stayed during the whole lecture in this condition.

Jundell was eminently industrious and was so fascinated by the problem he was studying that he forgot everything, even to eat and to sleep. When he and his friend Johan Almquist were training themselves in the accurate technique of the Wassermann reaction, he worked for two days and two nights without any sleep. He was very critical and strict with regard to his own writings, and corrected and rewrote his manuscripts over and over again before he was satisfied with them. When he became older, he began to suffer from writer's cramp and had increasing difficulty in writing by hand. As he never had used a typewriter before, he had to start teaching himself the art of typing at 70 years of age.

When he was very busy on working days, food and drink did not interest him at all. He was very irregular with his meals except dinners, which he took at 9 P.M., a dinnertime extremely late for Swedish customs. His principle was that people should live a simple life. His housemaids accepted this rule in their own way and Isak's standard of living became lower and lower; this fitted the lazy housemaids best. Isak did not recognize this and if he had, he probably would not have minded. Few men with Isak's high income got such inferior food as he did.

For his patients Isak would sacrifice almost anything. If he were called

upon, no time of the day was inconvenient, and no distance was too great. He never took a taxi when he visited a sick child within the boundaries of the city. He was beloved by his patients and he was especially kind and tender to those who were old and poor. His fees were very modest and he did not mind if he received no payment at all. When he died it was found that he had 70,000 crowns in unpaid bills—a large sum for Swedish conditions.

Jundell always stressed that a physician should train himself to use as simple tools as possible. He had no secretary, and no nurse attended him at his office hours; he performed all the necessary laboratory work himself.

He loved his home and was especially fond of antiques. When he had acquired a new piece, he put all his soul into trying to find the most fitting place for the object in his home. Frequently he had to rearrange his furniture in order to get the best out of a newly acquired find. Such rearrangements were a kind of nightly enterprise.

Isak loved and was very generous to his sisters and brothers and their families. When his mother died, he took care of his youngest sister, then 14 years old. She lived in his house, and he provided her with the best education available to obtain the vocational training that she wanted. Another of his sisters, married to a merchant in Finland, became a widow early and lost all of her fortune in connection with the Finnish revolution in 1918. Isak took the entire responsibility for this sister and gave her three children the opportunity to go to good schools and the son to qualify as a dentist.

Shortly after his retirement as professor he was invited to Great Britain. En route I met him at the railway station in Gothenburg where he arrived on the night train from Stockholm. He told me that he had spent an uneasy night due to bad dreams. He dreamt that he had entered his old lecture room and found all the seats except one occupied by students, pupil nurses, and doctors. Quietly he sat down on this spare chair to listen to the lecture but was immediately rebuked by a young pupil nurse who pushed him from the chair, telling him rather brutally that it was forbidden for him to sit, because the chair was reserved for Doctor X (a potential enemy of Isak Jundell). I suppose that this dream shows the inferiority complex of Jundell and his unhappiness at having lost his position in the clinic.

Several times I had the opportunity of accompanying Jundell on his visits to Germany in order to attend the annual German Congress of Pediatrics. He knew all the top men who were his good friends, and he was much honored by them and was often chosen as vice-chairman. He attended all the sessions and the entertainments, although he did not really enjoy the latter. He preferred modest hotels and never took his meals at big renowned international restaurants but in simple, popular, preferably Jewish places, and chose generally the cheapest dishes. He seemed to like to live as his poor father did while he was in Germany, before he emigrated to Sweden.

Arvid Wallgren

Comments on Current Literature

SERIOUS COMPLICATIONS OF VARICELLA, INCLUDING FATALITIES

CHICKEN POX, as a rule, is a benign childhood disease. However, because of possible complications, and because the virus has a tendency toward wide visceral spread, serious or fatal illness may result. A recent comment (February, 1957)[1] concerning varicella pneumonitis summarized reports appearing in current journals which seem to indicate that this complication of chicken pox may be more common, at least in adults, than is generally supposed, and that the mortality rate is significant.

Wide dissemination of the varicella virus in the body is evidenced by well-documented instances of visceral involvement; in addition to pneumonitis, nephritis, pancreatitis, myocarditis, and orchitis with subsequent testicular atrophy have been recorded. On the basis of necropsy studies, the visceral manifestations observed clinically were attributed to direct involvement of the respective tissues by the viral agent, eosinophilic intranuclear inclusion bodies being observed in the tissues of the liver, spleen, pancreas, adrenal glands, kidney, lung, lymph nodes, and in at least one recorded instance in the pericardium.[2] Hackel[3] (1953) reported myocarditis associated with varicella in seven patients, six children and one young adult, all of whom had experienced known contact and had clinical varicella at the time of death. Post-mortem studies revealed focal interstitial inflammatory lesions in the hearts of all seven patients. In many of the viscera, intranuclear inclusion bodies were identified, and in the case of one patient these inclusion bodies were observed in the pericardial tissue.

Central nervous system involvement in varicella seems to follow the same general pattern as that observed in other postinfection encephalitides. Autopsy studies classify the pathology of varicella encephalitis as broadly comparable to that of rubeola, and rubella, and as carrying a similar risk. The pathologic process is predominantly demyelinating in type, damage to the myelin varying from perivascular loss in the white matter to frank necrosis. Inflammatory perivascular infiltration with round cells or fat-containing phagocytes is a consistent finding, and degenerative changes in the neurons have been recorded. The over-all fatality rate has been given as of the order of 5 per cent, being somewhat higher in males than in females; older subjects with the exanthem seem more prone to central nervous system involvement.

A recently defined syndrome is that of varicella and severe hypoglycemia with convulsions. Wright, Lipson and Mortimer[4] describe three infants with varicella, ranging in age from 3 to 6 months, who developed hypoglycemia suddenly between the fourth and sixth posteruptive days. Two of the patients were admitted to the hospital "with varicella and severe intractable seizures, shown to be associated with hypoglycemia, and died within 24 hours,"[4] despite intensive therapy. The third infant suddenly

developed hypoglycemic seizures thirteen hours after treatment was instituted. Autopsy study in each instance revealed cerebral congestion, and in two of the three cases, cerebral edema. No demyelinization was apparent, and the pathologic changes in all three instances differed from those usually observed in varicella encephalitis. The age of the patients and the suddenness and severity of the hypoglycemic episodes were considered striking by these authors, who suggest that this occurrence of hypoglycemia in varicella raises interesting questions as to their relationship.

Thrombocytopenic purpura associated with chicken pox has been reemphasized within the past few years, several severe cases and one death being recorded.[5] This condition, which is known to follow many different types of infection, has been explained chiefly on the basis of hypersensitivity or antigen-antibody mechanism. Recent studies have stressed the importance of platelet antigenicity, and the suggestion was made that platelets altered by infection might react in this abnormal manner.

The *American Journal of Pathology* (issue of September-October, 1956) carries an interesting and very informative report by Cheatham, Weller, Dolan, and Dower.[6] This report concerns two fatal cases of varicella, and includes necropsy, virus isolation and serologic studies. The authors point out that "Although much has been learned regarding the pathogenesis of varicella, further progress in the understanding of this disease and its relation to herpes zoster has awaited the development of methods for the isolation and propagation of the etiologic agents."[6] During the past few years such methods have been devised in their laboratory, the work particularly of Weller and his associates.[7] These methods include the isolation of virus (varicella from the cutaneous eruption) by means of human tissue culture, and "immunologic procedures such as the fluorescent antibody technique," as well as the development of a complement fixation test. In the study of the two fatal cases of varicella "these techniques were employed together with the pertinent clinical and postmortem findings."[6]

The first of these patients was a 4-year-old boy who, about two months previously, had been treated for adrenal gland neuroblastoma by surgical excision and roentgen therapy. About three weeks previously, evidence of metastasis became apparent, and the child was placed on therapy with methotrexate (4-amino-N-10-methyl pteroylglutamic acid). While he was receiving this therapy for disseminated neuroblastoma the child developed varicella, having been exposed to three siblings in all of whom the course of the disease was typical and without complications. The exanthem in this boy appeared first on the face and spread to all parts of the skin, with lesions appearing also in the mouth. Vesicles continued to appear for seventeen days. Tumor therapy with methotrexate had been discontinued on admission to the hospital. Death occurred fifteen days following the onset of the eruption.

The second case was that of a 7-year-old girl who was receiving cortisone therapy for acute rheumatic fever. This patient had been on cortisone for four weeks at the time of onset of the eruption, "a pleomorphic vesicular rash" appearing on the trunk, back, and face eighteen days following known exposure to varicella. In this patient the course was fulminating, death occurring on the fourth day of the rash.

The pathologic studies and laboratory investigations carried out in connection with these two fatal cases are of considerable interest. In both cases the pathologic changes observed at autopsy were essentially similar to those reported in other fatal cases of varicella.[2] Focal areas of necrosis

containing type A intranuclear inclusion bodies were found in many organs, particularly in the skin, liver, lung, spleen, adrenal glands, gastrointestinal tract, and pancreas. In discussing the pathogenesis in their cases, the authors call attention to the involvement of the vascular epithelium in internal organs, to the fact that this type of involvement is mentioned in other necropsy descriptions of fatal cases,[2] and that intranuclear inclusions in the vascular epithelium are described in the early classic account by Tyzzer (1906) of the skin lesions in varicella.

The two fatal cases reported by Cheatham, Weller, and their associates have certain individual distinctions. The first case "presented a clinical picture consistent with severe chicken pox but had at necropsy a typical zosteriform eruption in addition to the disseminated varicella lesions. The dorsal root ganglion supplying the dermatone, as well as three other ganglia examined, showed intranuclear inclusions. Neural involvement was seen also in the small intestine, where there were many inclusions in cells of the myenteric plexus. Although involvement of the dorsal root ganglia may be the result of viremia, the simultaneous involvement of these ganglia and the myenteric plexus is also consistent with a neurogenic spread of the virus."[6] This first case was considered unusually "chronic," with immune response absent or slow in developing, since the vesicular eruption continued, antibodies could not be demonstrated, and since the virus was recovered from the blood at the time of death. In the average case of varicella, according to the work of these investigators, complement-fixing antibody appears about the fifth day of illness and rapidly reaches a high level. By tissue culture methods virus was isolated from the blood, vesicular fluid, and from lung tissue taken at autopsy.

The second case in a patient with acute rheumatic fever was distinguished by a fulminating course of short duration, by the remarkable "severity of the vascular damage with edema and widespread hemorrhage. The vascular endothelial cells were swollen in most organs, though inclusion bodies were seen only occasionally within them. Extensive and severe vascular involvement was observed in the sinusoids of the spleen where inclusion bodies were numerous. The focal hemorrhages were associated with definite evidence of local viral infection. The more diffuse endothelial damage may represent a stage of the same process. In view of the frequent association of severe cases of chicken pox with leukemia, the identification of inclusion bodies within what appeared to be lymphocytes is of particular interest."[6] In this patient, whose course was fulminating, the absence of complement-fixing antibodies at the time of death was not an unexpected finding. By means of tissue-culture preparations varicella virus was recovered from the blood and from the vesicular fluid. A third fatal case similar to the second was seen more recently by Weller and his associates[6]; in this patient also circulatory collapse was a prominent clinical feature.

This unusually rewarding study of two fatal cases of varicella integrates information gleaned from clinical observations, from pathologic findings, virus isolation, and serologic tests, and contributes to our knowledge of this common childhood disease in a manner not possible heretofore.

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REFERENCES

1. Blattner, R. J.: Varicella Pneumonia, Comments on Current Literature, J. PEDIAT. **50**: 258, 1957.
2. Johnson, H. N.: Visceral Lesions Associated With Varicella, Arch. Path. **30**: 292, 1940.
Oppenheimer, E. H.: Congenital Chickenpox With Disseminated Visceral Lesions, Bull. Johns Hopkins Hosp. **74**: 240, 1944.
Grayson, Chas. E., and Bradley, E. J.: Disseminated Chickenpox (Pneumonia and Nephritis), J. A. M. A. **134**: 1237, 1947.

Wesselhoeft, Conrad, and Pearson, C. M.: Orchitis in the Course of Chickenpox With Pneumonitis, Followed by Testicular Atrophy, New England J. Med. **242**: 651, 1950.

Eisenbud, Mark: Chickenpox With Visceral Involvement: Case Report, Am. J. Med. **12**: 740, 1952.

Kaplan, L., and Tully, J. B.: Visceral "Viral" Dissemination in a Patient With Bronchogenic Carcinoma, Arch. Path. **56**: 312, 1953.

3. Hackel, Donald B.: Myocarditis in Association With Varicella, Am. J. Path. **29**: 369, 1953.
4. Wright, Elmer M., Lipson, M. J., and Mortimer, Ed. A., Jr.: Varicella and Severe Hypoglycemia: A Previously Undescribed Syndrome, A. M. A. Am. J. Dis. Child. **92**: 512, 1956. (Abst.)
5. Welch, R. G.: Thrombocytopenic Purpura and Chickenpox, Arch. Dis. Childhood **31**: 38, 1956.
6. Cheatham, W. J., Weller, Thos. H., Dolan, T. F., Jr., and Dower, J. C.: Varicella: Report of Two Fatal Cases With Necropsy, Virus Isolation, and Serologic Studies, Am. J. Path. **32**: 1015, 1956.
7. Weller, Thos. H., and Stoddard, M. B.: Intranuclear Inclusion Bodies in Cultures of Human Tissue Inoculated With Varicella Vesicle Fluid, J. Immunol. **68**: 311, 1952.

Weller, Thos. H.: Serial Propagation in Vitro of Agents Producing Inclusion Bodies Derived From Varicella and Herpes Zoster, Proc. Soc. Exper. Biol. & Med. **83**: 340, 1953.

Weller, Thos. H., and Coons, A. H.: Fluorescent Antibody Studies With Agents of Varicella and Herpes Zoster Propagated in Vitro, Proc. Soc. Exper. Biol. & Med. **86**: 789, 1954.

Weller, Thos. H., and Witton, H. M.: Unpublished data (quoted reference 6).

MEDICAL EDUCATION WEEK

APRIL 21-27, 1957

THE week beginning Easter Sunday has been designated as *Medical Education Week* by the sponsoring organizations: The Association of American Medical Colleges, The American Medical Association, The American Medical Research Foundation, and the National Fund for Medical Education. The purpose is to bring to the public the story of the progress made by the medical schools in the education of physicians, medical research, and community service. It deserves the support of every physician, as it was the medical school that made it possible for him to become a doctor. We urge pediatricians to support and take an active part in the local plans for Medical Education Week being developed in many communities.

There are a number of facts regarding medical education with which the average physician is not too familiar as well as a number of erroneous ideas held by the public. For this reason we present a few of the facts.

There are today eighty-two approved medical schools in the United States. Seventy-six of these have a full four-year course leading to the M.D. degree, while six conduct only the first two basic years. Six of the seventy-six four-year schools are of recent development, graduating their first class in the years 1957 to 1960 (Mississippi, Missouri, West Virginia, Einstein, Seton Hall, and Florida). Three of these have expanded from two-year schools and three are completely new.

One of the questions frequently raised is whether the medical schools are graduating sufficient physicians to meet the needs of our steadily increasing population. In 1930 the medical school enrollment was 21,597. By 1954 the enrollment had reached 28,639, an increase of 32.7 per cent in twenty-five years. In 1930 the number of doctors graduated was 4,565. In 1954 the number graduated was 6,845, an increase of 50 per cent. Both percentage figures are greater than the 25 per cent increase in our population during this period. The number of doctors has increased 120 per cent, and the medical school enrollment, 128 per cent since 1910, compared with a population increase of 80 per cent. Today in the United States there is one doctor for every 730 persons in our population. Except for the newly formed state of Israel, to which so many physicians from other countries have migrated, this is a lower ratio than is found in any other country in the world.

Another subject often discussed, more emotionally than with knowledge, is the admission of students to the medical schools. Quite wild statements are sometimes made as to the impossibility of vast numbers not being able to gain admission for one reason or another. Here confusion

exists between "applicants" and "applications." In 1954-1955 there were 14,536 applicants, who made 47,568 applications. Thus the average applicant applied for admission to over three different medical schools. Of the 14,538 applicants, 7,576, or over 50 per cent, were admitted.

Another fallacy in this connection is the frequently heard statement that only a man or woman with an "A" scholastic grade in college can gain admission to a medical school. The premedical scholastic grades of those admitted in the class of 1954-1955 were as follows:

17 per cent had an "A" average
69 per cent had a "B" average
14 per cent had a "C" average

The medical schools have found by experience that the well-rounded man or woman will probably make a better doctor than the "grind" who simply works for and obtains high passing grades. While scholarship and intellectual capacity are most important, medical school admission committees and officers have learned to look for something far more than college grades in screening the applicants. By intensive studies in the selection of students admitted, the medical schools have learned how to keep the "failure rate" low. Only 231 (3 per cent) failed in scholarship of the 7,686 admitted to the first-year class in 1955-1956, and four of the 6,886 who had reached their fourth year. Many applicants have no real qualifications for admission to a medical school except a desire to study medicine.

The eighty-two medical schools are about equally divided between private and tax-supported schools, forty-two to forty, and the student enrollment is about equally divided. The tax-supported schools (mostly by state governments) tend to enroll students from their own state. Thus in this group of forty schools, only 9 per cent of the enrollment is from outside the state in which the school is located, as contrasted with 53 per cent of the enrollment in the private schools. Three-fourths of the total applications for admission are made to the private schools and only one-fourth to the tax-supported schools.

Medical education is the most expensive form of education of all the various disciplines. While the average tuition paid by the student is over $800 a year, the total tuition fees meet less than one-fifth of the cost of operating the medical schools.

The estimated operating budgets of the eighty-two schools for 1956-1957 amount to $111,167,673, and the sources of this sum are as follows:

Government (State, Municipal, Federal)	$52,701,162	47.5%
Income from endowment	12,775,283	11.5%
Tuition fees	20,305,535	18.2%
General university funds	7,507,980	6.7%
Gifts and grants	17,877,713	16.1%
	$111,167,673	100.0%

This is the total picture and not the percentage distribution for any one school. Only forty-nine of the eighty-two received tax funds, fifty have endowment income, and thirty-five receive support from the general funds of the university of which they are a part.

It is also the most expensive type of education for the individual, with the many necessary years of college,

medical school, and graduate education, before any financial return is possible.

The above discussion applies to the medical school in connection with undergraduate education. The medical school has additional functions. With the complexity of modern medicine resulting from the advances in scientific knowledge and techniques, it has become impossible for a physician to master all of medical science. This has led to a rapid increase in specialization, the development of groups of physicians particularly qualified by their training in some one field or branch of medicine. In addition to the undergraduate training, the medical school has had to assume a large part of the responsibility and cost of training our surgeons, pediatricians, and a dozen or more other types of specialists.

Medical progress is dependent on medical research. Research is one of the most important functions of a medical school. In its laboratories and hospital wards, new diagnostic methods, new methods of treatment, the testing of new drugs, along with many other research projects of a more basic nature, are being studied and carried out intensively as a routine day-by-day activity.

As stated the purpose of Medical Education Week is to try and bring before the general public the story of our medical schools. It should have the active and wholehearted support of every physician.

Correspondence

To the Editor:

I greatly enjoyed your editorial "Are Medical Meetings Worth While?" The big ones formerly were excellent for young eager beavers who wished to see the men of whom they had read. Nothing could surpass my first medical meeting in Atlantic City at which Dr. Welch pointed out Dr. Zinsser, Dr. Flexner, and the other leaders in medicine.

Now the big medical meetings are so large that we rarely see our friends, and most of the papers are presented by the younger generation who were onlookers in our era. They speak a language quite unintelligible to most of us. I recently came out of a big meeting in Atlantic City with two professors of medicine. One turned to the other and said, "That was a rotten paper." The other man said, "Why?" The first man said, "Because I understood it."

The greatest present benefit of attending the big meetings is the study of the scientific and commercial exhibits. Every physician can learn a great deal from both and learn it "visually" instead of the more languorous auditory method. The attendance at medical alumni dinners during these big meetings is also a great source of pleasure.

However, I wish to point out the value of the smaller meetings of county, district, and state medical societies and of regional associations, such as the Seaboard Medical Association and the Tri-State Medical Association. They are particularly valuable for those of us who teach in "ivory towers" in order that we can keep in touch with the men actually in practice and not only learn a great deal of sound medicine from them, but also they keep our teaching on a more practical basis.

In attending small medical meetings, a medical faculty has the opportunity of collecting complaints, correcting misunderstandings and explaining admission and other policies, making friends and improving public relations. It is far more pleasant for a medical faculty to deal with friends thus made than members of the medical profession who are suspicious of the intentions of a medical school.

In addition, the referring of patients to a teaching hospital is an important product of the teaching staff's attendance at these meetings. With the hundreds of Hill-Burton hospitals being built throughout the country, the American teaching hospitals may soon be in the same situation as the London teaching hospitals which are now in competition with the new county and state supported hospitals. The medical school faculties should keep in close touch with the practicing medical profession so that they can know our needs and problems and we theirs.

W. C. DAVISON

To the Editor:

Your anonymous reviewer (J. PEDIAT., December, 1956) of my monograph *Masked Epilepsy* does not measure up to your high standard of fairness.

I will not quarrel with his right to form his own opinion about the value of my evidence, and he is obviously entitled to say that he thinks it is inadequate without giving his reasons.

But a reviewer has duties as well as rights, and one of them is to read the work he is reviewing. I made it quite plain that the monograph was developed from and included parts of a paper published in *The Lancet* (1: 70, 1955), and that similar ideas had been put forward by other workers in such journals as *Pediatrics, The Journal of the American Medical Association, The Annals of Internal Medicine,* and even THE JOURNAL OF PEDIATRICS.

Yet your reviewer says: "Probably the reason for the presentation of his theory in monograph form lies in the ideas and theory being so unsupported by evidence or proof that they would not be acceptable for publication in most medical journals."

I should like to add now that the Editor of *The Lancet* in an annotation (1: 91, 1955) wrote favorably of my work, and in a private letter has encouraged me to put the work in monograph form. I have had over 100 requests for reprints from all over the world, including America.

I think therefore that there is enough evidence to show that these ideas are not negligible nor unsuitable for publication.

H. R. E. WALLIS, M.D.

News and Notes

Dr. Aims McGuinness of Philadelphia has been appointed Special Assistant for Health and Medical Affairs to Secretary Folsom of the Department of Health, Education and Welfare. He took over his new duties in Washington early in January. Dr. McGuinness will continue as Secretary-Treasurer of the American Pediatric Society. His address for Society affairs is Room 1036, 2800 Quebec Street, N. W., Washington 8, D. C.

On Feb. 27, 1957, the Frederick H. Allen Building at the New Jersey Neuro-Psychiatric Institute, Princeton, N. J., was dedicated. George E. Gardner, M.D., Director of the Judge Baker Guidance Center, Boston, Mass., and Professor of Child Psychiatry at Harvard University, delivered the principal address. The building is named in honor of Frederick H. Allen, M.D., who was Director of the Philadelphia Child Guidance Clinic for thirty years until his retirement in 1956. The Allen Building will accommodate over 100 patients in the Children's Unit at the Institute, who are presently housed in two older buildings.

The **Sixth Annual Clifford D. Sweet Seminar** will be held on June 7 and 8, 1957, at the Children's Hospital of the East Bay in Oakland, Calif. The guest speaker will be Sydney S. Gellis, M.D., Professor of Pediatrics, Boston University School of Medicine, Boston, Mass.

The **Summer Camp for Diabetic Children** will be opened for the eighth season under the auspices of the Chicago Diabetes Association, Inc., from July 14 to Aug. 4, 1957, at Holiday Home, Lake Geneva, Wis. In addition to the complete camp personnel, the Diabetes Association furnishes a staff of resident physicians and dietitions, trained in the care of diabetic children. Boys and girls, ages 8 through 14 years, are eligible. Physicians are urged to notify parents of diabetic children and to enter the names of children who would like to attend camp. Further information as to fees, applications, etc., may be obtained from The Chicago Diabetes Association, 5 S. Wabash Ave., Chicago 3, Ill. Limited capacity requires prompt application.

The following recommendation recently adopted by the Advisory Committee to the New York City Department of Health Poison Control Center is of general importance and interest, as one of the major emergencies faced by physicians is the treatment of accidental and suicidal ingestion of overdose of drugs, especially massive overdosage in children.

"The Poison Control Center Advisory Committee recommends that, wherever possible, the pharmaceutical company should, in its brochure and package circulars to physicians on new drugs, describe briefly: the maximum therapeutic dose; the dosage level of serious toxicity, particularly in children; symptoms and signs of massive overdosage; treatment."

At present, side reactions, contraindications, and toxicity in normal therapeutic quantities are discussed by drug manufacturers in professional literature and in the directions for use. However, it is only occasionally that massive overdoses have been discussed.

The **Fourth International Poliomyelitis Congress** will be held at Geneva, Switzerland, July 8 to 12, 1957. Among the subjects for discussion are vaccination against poliomyelitis, enteric viruses producing disease simulating poliomyelitis, basic problems of respiratory distress, and the care of patients with severe poliomyelitis. Active membership is open to physicians and scientists. Hotel reservations should be made through local representatives of the American Express Company, Thos. Cook & Son or Wagons-Lits Cook. Registration should be made by April 1, 1957, through the Secretariat: Hotel du Rhone, Geneva, Switzerland. No registration fee.

The **Ninth Annual Summer Clinics** of the Children's Hospital in Denver, Colo., will be held June 24, 25, and 26, 1957. Guest faculty this year will be Dr. Stewart H. Clifford, Assistant Clinical Professor of Pediatrics, Harvard Medical School, Dr. H.

William Clatworthy, Jr., Associate Professor of Pediatric Surgery, Ohio Medical University, and Dr. Edith L. Potter, Professor of Pathology, Department of Obstetrics and Gynecology, The University of Chicago. Further information can be secured by writing the Chairman, Summer Clinics Committee, Children's Hospital, Denver 18, Colo.

The **Cook County Graduate School of Medicine** announces an intensive course in the *Neuromuscular Diseases of Children*, with special emphasis on cerebral palsy, to be given by Dr. Meyer A. Perlstein for the two-week period from July 8 to 19. For further information, write to John W. Real, Registrar, Cook County Graduate School of Medicine, 707 S. Wood St., Chicago, Ill.

Residency positions in *Pediatric Pathology* are available for the year 1957-1958 at the **Children's Hospital, Columbus, Ohio,** in the Pediatric Pathology division of Ohio State University, School of Medicine. Approximately 350 autopsies and 3,000 surgical specimens are studied per year and provide the basis for a well-rounded experience in newborn, infant, and child anatomic pathology. The service is designed to train either pediatricians or pathologists, who desire a year of intensive experience in this field, and is approved for residency training. Depending on the interests and desires of the applicant, these appointments could also include experience in pediatric hematology, clinical pathology, or both. The stipend ranges from $150 to $300 per month, depending on the applicant's previous experience. Those interested in further details should write: W. A. Newton, Jr., M.D., Director of Laboratories, Children's Hospital, Columbus 5, Ohio.

The following short refresher courses will be given at **The Children's Hospital of Philadelphia** in May and June, 1957.

Pediatric Advances for Pediatricians and General Practitioners. May 27 through May 31, 1957. Conducted by the Staff of the Children's Hospital of Philadelphia, in collaboration with the Department of Pediatrics of the University of Pennsylvania and the Staff of the Camden Municipal Hospital.

Practical Pediatric Hematology. June 3, 4 and 5. Conducted by Irving J. Wolman, M.D., and other members of the Hematology Department of the Children's Hospital, under the auspices of the Graduate School of Medicine, University of Pennsylvania.

Blood Group Incompatibilities and Erythroblastosis Fetalis. June 6 and 7. Conducted by Neva Abelson, M.D., and Thomas R. Boggs, Jr., M.D., of the Philadelphia Serum Exchange of the Children's Hospital of Philadelphia, under the auspices of the Graduate School of Medicine, University of Pennsylvania.

Inquiries should be addressed to Irving J. Wolman, M.D., Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46, Pa.

In order to encourage scientific work by young investigators and to show a small measure of appreciation for fruitful scientific effort, the Ross Laboratories have established a *Pediatric Research Award.*

Each year the Western Society for Pediatric Research will confer this award on a chosen nominee in recognition of outstanding research accomplishment in a field related to pediatrics. The nominee shall not be over 35 years of age, and during the progress of his research shall have resided for at least one year in the geographic area represented by the Society. The work need not have been published. The award consists of $1,000 and a suitably engraved plaque to be presented to the nominee at the annual meeting of the Society.

Nominations may be tendered by any member of the Western Society for Pediatric Research. Nominations should be submitted in quadruplicate and include all supporting data and a clear statement of the reasons why the candidate is considered worthy of the award, designating the particular aspects of his work which are considered outstanding. *Nominations will close April 30* in order to give the Committee sufficient time to come to a decision prior to the annual meeting in the fall. The award may be given jointly to two or more investigators at the discretion of the Committee, or it may be omitted if the Committee considers that a worthy candidate has not been presented. Please mail directly to Robert H. Alway, M.D., Secretary-Treasurer, Western Society for Pediatric Research, 2351 Clay St., San Francisco, Calif.

Books

Physical Measures in the Treatment of Poliomyelitis. Robert J. S. Reynolds, M.C.S.P., New York, 1956, The Macmillan Co., 140 pages. Price $2.50.

A small text, or manual, presenting the methods used in the treatment of patients at the poliomyelitis unit at Queen Mary's Hospital, Carshalton. Considerable stress is placed on the use of wet packs in the acute stage to reduce spasm and prevent deformity. The text then goes on to discuss muscle testing, re-education movements, appliances, and the principles and objectives of surgical measures. It is a large, well-known clinical unit, and workers interested in the rehabilitation of patients with paralytic polio will find the text interesting and useful.

Le Traitement de la tuberculose de l'enfant. International Center for Infancy, Paris, 1956, Masson et Cie, 353 pages. Price 2,500 Fr. francs.

Proceedings of a seminar on the treatment of tuberculosis in the infant, held in Paris, December, 1955, by the International Center. Prof. R. Cruchshank of London was chairman. Some eight topics were discussed, including the treatment of the initial pulmonary lesions, bacteriologic problem, and the treatment of acute miliary and tuberculous meningitis. Specialists in the field from a number of countries were in attendance and took part. The book contains the papers presented, together with the discussions. Unfortunately, the lack of an index detracts considerably from its usefulness.

L'Asystolie primitive chez l'enfant. Docteur Guy Lascombes, Nancy, 1956, Imprimerie Berger-Levrault, 146 pages.

A monograph by the chief of the children's clinic in Nancy on "l'Asystolie primitive" which he considers a clinical entity. After an acute or gradual onset, often afrebrile, with vomiting and pulmonary involvement, signs of definite cardiac insufficiency become apparent: tachycardia, gallop rhythm, and enlargement of the heart clinically and roentgenologically. The author bases his study on forty-four personal cases observed at the clinic. Pathologically there is an acute myocarditis, and in some cases endocardial fibroelastosis is present. The etiology is unknown, but the author considers the possibility of a virus infection. Treatment symptomatic.

Le Traitement des angiomes chez les enfants. Simone Labordi, Paris, 1956, Masson et Cie, 174 pages. Price 1,850 Fr. francs.

This text will be of particular interest to the radiologist. After a short chapter on the clinical varieties of angioma the author takes up in detail the various methods of treatment by roentgen ray, radium, thorium, as well as injection methods. Considerable stress is placed on the complications of radiation and their avoidance. The text is well illustrated. It is a very practical book based on a large experience.

Amino Acid Handbook. Richard J. Block, Ph.D., Springfield, Ill., 1956, Charles C Thomas, Publisher, 386 pages. Price $10.50.

With the increasing interest in the amino acids this handbook will be of great value to those working in the field. It describes the technical methods of chemical and microbiological analyses and the determination of the amino acids in protein by paper and column chromatography. Another chapter presents the data on the amino acid requirements.

Paper Electrophoresis. Proceedings of a Ciba Foundation Symposium, Boston, 1956, Little, Brown & Co., 224 pages. Price $8.00.

Some twenty-two scientists from a number of different countries participated in the symposium in July, 1955. With the increasing importance of electrophoresis as a diagnostic tool, the bringing together of a group prominent in the field to discuss methods and its use in research and clinical medicine was most timely. Some eighteen papers appear in the report together with the discussion.

Editor's Column

THE PHARMACEUTICAL INDUSTRY AND MEDICAL PRACTICE

WE WONDER how many physicians realize the extent to which the pharmaceutical industry, whose interests in so many ways are a part and parcel of medical practice, has become what is popularly designated these days "big business." For many years the "ethical" drug business was regarded in financial circles as a rather sound but unexciting and small segment of industry. Not a few companies were "family corporations." The picture has changed. Some companies once family owned, such as Mead-Johnson and Lilly, expanded and became publicly owned corporations. Some, such as Parke-Davis and Lilly, have remained independent, while others have been bought or absorbed by large chemical companies with tremendous financial resources, whose total sales run over a half billion dollars a year. Thus Squibb is a division of Olin Mathieson (which incidentally manufactures killing products as shotgun ammunition), and Lederle of American Cyanamid. The setup of American Home Products is even more interesting. It owns the Wyeth and Ayerst companies, which function as an "ethical division," producing products for the physician to use and prescribe, but in addition has a "proprietary division" [why not "unethical"?] which makes, advertises, and sells such drugs as Anacin direct to the public for self-medication. The gross sales of most of the pharmaceutical companies have increased tremendously in recent years. The sales of the Pfizer and of the Lilly companies, for example, are reported to have been around $180 million in 1956, and the Lederle division is said to account for over 25 per cent of American Cyanamid sales. The sale of antibiotics by nine major drug companies was estimated at $260 million in 1955. The annual report for 1955 of one of the highly respected companies states gross sales of around $125 million. The *cost* of the products sold is reported as around $50 million. Taxes were between $14 and $15 million. The item for research and product development comes to over $4.5 million. Selling (which includes advertising and detail men), together with administration and general expenses, is an item over $38 million. We doubt if the financial statements of other companies would show much variation in a breakdown.

We have no objection to the "profit motive." It is responsible for the remarkable economic development of this country. Further, we fully recognize the tremendous importance of the many valuable products which the pharmaceutical companies have

developed in recent years and have made available to physicians for the treatment of their patients. All we have in mind is an attempt to describe a little of what has taken place in the industry.

The present position of the pharmaceutical companies in the financial or commercial world is well illustrated by the fact that in the last two or three years the first information regarding new drugs or products has not infrequently come to us from financial journals or sources, rather than through medical sources as one might naturally expect. A number of months ago we noted the stock quotation of a certain pharmaceutical company was steadily rising.* Inquiry for the reason from a broker friend brought the information that the company was "bringing out a new quieting drug which it was thought would make a lot of money." This was our first news of their "tranquilizer." The financial and investment circles were right, as the profits of this company increased 50 per cent in 1956 over the previous year. In the *Wall Street Journal* of Nov. 1, 1956, we read how Lilly had suspended tests of Carbutamide after fifteen months' trial because 5 per cent of the diabetics had developed serious side effects. It was weeks later before we saw the same information in a medical publication. In that same issue was a "box" item, "by a Wall Street Journal Reporter," stating that Parke-Davis had applied for a license to market a vaccine for the treatment of the common cold. In *January* of this year we read a report made by an official of a pharmaceutical company before a group of the Society for Security Analysts which stated that the company was bringing out a new, improved sulfa drug in *March*. Even the trade name was given. *Barrons*, last November, had a most informative article entitled "Broader Spectrum," discussing the field of the antibiotics. Another very informative article in a December issue of *Barrons* was entitled, "Peace of Mind," with the subheading, "Makers of Tranquilizing Drugs Enjoy a Healthy Rise in Sales." Healthy! It told in detail how starting from scratch three years ago sales had built up to a volume of $135 million in 1956, were expected to double in 1957, and to reach between $400 and $500 million within the next three to five years. This item of expected growth is of considerable interest and importance to physicians in view of the increasing number of reports of side effects from some of the tranquilizing drugs. These few random examples of the present interest of the financial world in the products, sales, and profits of the pharmaceutical companies are cited solely for the purpose of illustrating what we mean by the statement that the ethical pharmaceutical industry has become "big business."

Some of the results of this development are of great significance in the present-day practice of medicine, as well as to the future of medicine. Research in pharmacology has been largely taken over by the drug firms in their search for new products, and this in turn has led to therapeutics—the treatment of the patient—being masterminded by the

*Lest there be any misconception of our personal interest, the Editor does not and never has owned a share of stock in a pharmaceutical company or in a company catering to the "infant trade."

pharmaceutical companies rather than by the medical school and medical educator. Our good friend, the detail man, has taken on the function of an instructor in therapeutics. Back of this development there is a fundamental change in motivation, a change from the nonprofit altruism of medical research to one of the profit motive. The commercial companies are pouring huge sums of money into research, a necessity in an industry which has become highly competitive, and a return to former conditions is quite out of the question. From financial reports and statements we learn that some companies are spending over $5 million a year on research, and the total sum is staggering. Naturally this is done with the expectation that by discovering and marketing new products the investment in research will be returned. For a time at least, until the competitors catch up, new products must and can be sold at a price high enough to cover the cost of the research, as well as the cost of the advertising campaign necessary to induce the physician to prescribe the new drug.

We do not wish to leave the impression that the research work of the pharmaceutical company laboratories is wholly commercial. We know of no more high-minded scientists than the directors of some of the research laboratories. They have not only made important investigations that seemingly are quite removed from any profit motive, but on many occasions have been most helpful in aiding research in the medical schools involving problems quite unrelated to therapy.

Seemingly the moment one firm produces a product that catches on, other companies try to develop a similar product to compete for the consumer's dollar. This can be done only if the physician in some way can be persuaded to use and prescribe the particular product of a particular company. Starting with only one company and drug in the so-termed "tranquilizer" group, six firms are now producing one or more drugs of a similar type and each claiming superiority in some aspect. The situation regarding the antibiotic group of drugs is far more complex.

There are many hazards in the pharmaceutical industry. It is not all a bed of roses and big profits by any means. The obsolescence rate is high. Huge sums are often expended for the production and testing of products, only to have to discard them, as in the case of Carbutamide mentioned above. In a way, it is somewhat similar to the exploratory well drilling of the oil industry which so frequently invests large sums in what turns out to be a dry well. From the financial standpoint a venture may turn out quite disastrously for a company, as the experience of the Cutter Laboratories with the Salk vaccine, although no evidence could be found that the company's laboratory was in any way at fault. The danger of a financial "kickback" is probably one of the best controls that exists over the quality and the safety of new products.

There are other medical issues involved, as the rather ludicrous avalanche of trade names recently discussed editorially in the JOURNAL.

Advertising has become at times a headache for those responsible for the medical journals. Most companies have every desire and intention of keeping their advertising clean and

honest. But, as was so aptly implied in a recent editorial in the *New England Journal of Medicine,* there are Sinners as well as Saints. The fierce competition that exists has led at times to exaggerated claims by copywriters for some particular product. One misleading advertisement is harmful to all. While each medical journal must be responsible for and can censor the advertising it accepts, there is no such control over the direct mail advertising flooding the doctor's office. While it is impossible to obtain data, the total sum allocated to direct mail advertising is undoubtedly much larger than that budgeted for advertising in the medical journals. The medical journal censorship varies considerably and at times seems somewhat unrealistic. One group of journals, for example, refuses to accept advertisements of multivitamin preparations, while others with equally high ethical standards, recognizing not only their almost universal use by physicians and the fact they are recommended in the texts on infant care, accept such advertising. There is not a single medical journal that has not made mistakes and is in a position to boast of superior high-mindedness in the matter of advertising. Nearly all, we are certain, are impelled by the same high motives in their decisions, even if they do vary.

Scientific documentation of the value of a new drug is a problem that is growing by leaps and bounds with the rapid increase of new drugs plus those developed on a competitive basis. That the value of a new drug can only be determined by actual testing is obvious. However, with the multiplicity of new products it would seem as if many of our hospital clinics are becoming mere testing adjuncts for the pharmaceutical companies. All too often clinics and physicians are induced to make a so-called "scientific research study" of a new product, although quite unprepared by training and experience to undertake a research project. It results in papers being written extolling this or that product based on inadequate evaluation. Once such a paper is printed by a medical journal it serves as gospel for advertising purposes. Sound clinical evaluation studies are most important and should be published, as they furnish the only way the practicing physician can judge whether or not a drug measures up to the virtues claimed for it by the detail man. It is an obligation a medical journal owes its readers. Evaluation papers constitute a complex problem for an Editorial Board.

Complaints by the public of the high cost of the newer drugs are steadily increasing and cannot help but be an important factor in the future social and economic position of medicine.

The returns to the company must cover the cost of the research and the drug's introduction, as well as the actual cost of manufacturing and merchandizing the drug. If one adds the retail "markup" to the gross sales figures of the company quoted above, the average cost to the consumer is at least four to five times the cost of the ingredients and labor involved in making the products. Recently we had occasion to investigate one of the newer drugs against which no scientific objection could be raised. The only justifiable clinical

claim was that it was equivalent as an antipyretic with aspirin. The joker lay in the fact that its cost to the patient was eighteen times greater than an equivalent amount of aspirin.

We cannot see eye to eye with some of our medical colleagues who feel that the pharmaceutical industry should share its profits with the hospital clinics for purposes of research. It is not the pharmaceutical firms who would pay for such a subsidy, but rather the consumer through the cost to him of drugs. That such an indirect, concealed tax on the consumer can be regarded as ethical is a moot question. With the tremendous increase in Federal appropriations for medical research to which we all contribute through taxes and which is distributed in the form of many hundred specific research grants, is such an additional concealed charge to the consumer quite honest? The consumer must also pay for the so-termed "good relationship" expenditures of the pharmaceutical companies. Even this form of securing the physician's favor has become highly competitive, and some feel has gone quite out of bounds at medical meetings. In the final analysis it is an expense borne by the physician's patients.

The purpose of this discussion is simply to present certain aspects of the pharmaceutical industry and its relationship to medical practice. Seemingly from many discussions with medical friends there is little awareness of what has happened and of some of the problems which have followed in its wake. We recognize the tremendous value of the contributions to therapy made by the ethical drug companies in recent years. The pharmaceutical industry and the medical profession are closely interwoven, and each is dependent upon the other. The problems that have developed need working out to the satisfaction of both. From personal experience we have found difficulties are often due to misunderstanding. It is our feeling that if representatives of the industry—policy-making, sales, and advertising agencies—could sit down with representatives of the medical profession—societies, medical editors and publishers—it would be profitable for both. It would be interesting to try it out in a small informal way, and we venture the opinion it would lead to an expanded meeting on a larger, more formal scale. When two groups are so dependent upon one another as the ethical pharmaceutical companies and the medical profession, there must be a full understanding of the objectives and problems of each by the other.